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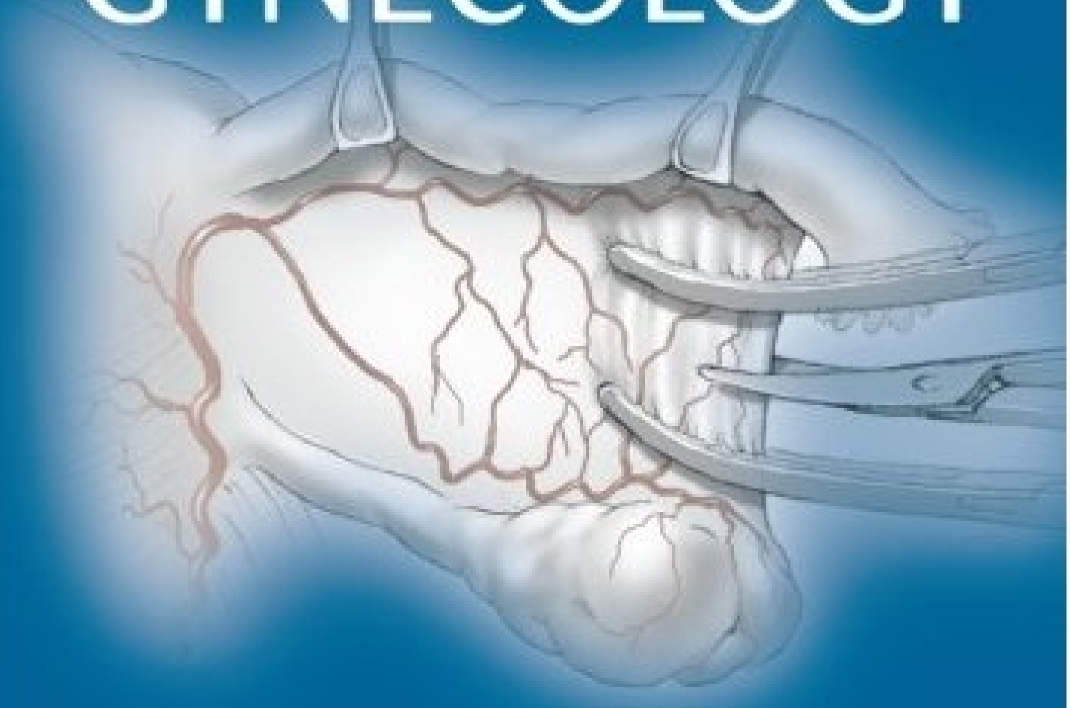
Williams GYNECOLOGY



Preface

The first edition of *Williams Obstetrics* was published over a century ago. Since then, the editors of this seminal text have presented a comprehensive and evidence-based discussion of obstetrics. Patterned after our patriarch, *Williams Gynecology* provides a thorough presentation of gynecology's depth and breadth. In Section 1, general gynecology topics are covered, whereas Sections 2 through 4 offer content on the gynecologic subspecialties. Of note, the developing field of female pelvic medicine and reconstructive surgery is presented.

Traditionally, gynecologic information has been offered either within the format of a didactic text or that of a surgical atlas. However, because the day-to-day activities of a gynecologist blend these two, so too do we. The initial five sections of our book describe the evaluation and medical treatment of gynecologic problems. The remaining section offers an illustrated atlas for the surgical correction of these conditions. Discussions of disease evaluation and treatment are evidence based, and our text strives to assist the practicing gynecologist and resident. Accordingly, chapters are extensively complemented by illustrations, photographs, diagnostic algorithms, and treatment tables.

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Artist renderings in our surgical atlas were produced by Lewis Calver, the Chairman of the Biomedical Communications Graduate Program, and students and faculty within that program.

The world's first degree in medical illustration was awarded by Southwestern Medical School in 1947. This is one of five accredited medical illustration programs in North America. For those accepted into the program, a Master of Arts degree in Biomedical Communicationsâ€”Biomedical Illustration is offered by Southwestern Graduate School of Biomedical Sciences at The University of Texas Southwestern Medical Center. The program is two years in length and a maximum of seven students is now enrolled annually.

The program is offered through the Department of Biomedical Communications, and courses are taught by faculty of The University of Texas Southwestern Medical School, Southwestern Graduate School of Biomedical Sciences, and Southwestern Allied Health Sciences School. The program is accredited by the Commission on Accreditation of Allied Health Education Programs and the Association of Medical Illustrators. Mr. Lewis E. Calver has been Program Chairman since 1980.

The program is interdisciplinary. It is designed to provide opportunities for development of special knowledge and skills in the application of communications arts and technology to the health sciences. Study of human anatomy, cell biology, neurobiology, and pathology is combined with experience in anatomical, surgical, editorial and advertising illustration, computer graphics and animation, graphic design, multimedia production, interactive computer assisted instruction, and instructional design. Additional skills may also be developed in biological illustration, three-dimensional media production, exhibit design, and photography.

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6/17/2008: HUMAN PAPILLOMA VIRUS AND HUMAN IMMUNODEFICIENCY VIRUS-INFECTED WOMEN

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Related To: Chapter 29. Preinvasive Lesions of the Lower Genital Tract

View in chapter

Overview

Human immunodeficiency virus (HIV) infected women are known to have a high burden of human papilloma virus (HPV)-associated anogenital disease. This lower genital tract disease manifests as a spectrum of lesions, which ranges from condyloma to high-grade, high-malignant potential cervical intraepithelial neoplasia (CIN), vulvar intraepithelial neoplasia (VIN), and anal intraepithelial neoplasia (AIN) lesions.

The association between cervical dysplasia, cervical carcinoma, and human papilloma virus (HPV) infection is clearly established (Bosch, 2002). However, the etiologic contribution of human immunodeficiency virus (HIV) in the development of lower genital tract disease is unclear and currently under evaluation. Specifically, areas of attention include the effect of HIV serostatus in the acquisition, regression, persistence, or progression of HPV infection. The relationship between HIV and HPV infections may involve mechanisms that integrate virus to virus interactions, immune factors, and molecular pathogenesis, and all of these mechanisms can impact normal cell cycle machinery (Clarke, 2001).

Although evidence to date establishes HPV as the etiologic agent causing cervical intraepithelial and invasive neoplasia (Mahdavi, 2005), HPV infection is generally uneventful and transient in HIV-seronegative women. In contrast, recent studies have shown that HIV-positive women have a higher prevalence and longer persistence of cervical HPV infection. HPV is detected in more than 60 percent of women with HIV (Stover, 2003). In addition, these women have a higher probability of carrying multiple oncogenic HPV types than that of HIV-negative women (Ahdieh, 2001; Brown, 1994; Palefsky, 1999).

The effects of HIV can also be seen in the rates of disease progression. For example, early during the acquired immune deficiency syndrome (AIDS) epidemic, Maiman and colleagues (1990) noted in a study cohort that all HIV-positive women with cervical cancer died from their cancer compared with only 37 percent of HIV-seronegative women with cervical cancer. Because of this and similar studies, cervical cancer is now designated as an AIDS defining condition by the Center for Disease Control and Prevention.

Lower Genital Tract Intraepithelial Neoplasia

Studies consistently suggest that HIV-positive women have much higher rates of CIN compared with HIV-uninfected women (Ellerbrock, 2000; Wright, 1994). For example, in women infected with HIV, up to 60 percent of Pap smears exhibit cytologic abnormalities, and as many as 40 percent have colposcopic evidence of dysplasia. Maiman and associates (1998) report that these rates are approximately 10 times greater than those observed among HIV-negative women.

In contrast, much less information is available regarding vulvar, vaginal, and anal intraepithelial neoplasia in these women. However, a recent 6-year prospective study did compare HIV-positive with HIV-negative women at high risk for HIV and found an eightfold increase in the rates of vulvar, vaginal, and perianal lesions in HIV-positive women (Jamieson, 2006). Moreover, Chin-Hong and associates (2005) found a higher prevalence of HPV-associated anogenital disease in women with HIV compared to age-

matched HIV-negative controls. Specifically, in women with HIV, higher rates of anal HPV infection and increased rates of infection with oncogenic HPV types have been noted (Palefesky, 2000; Sun, 1997). A cross-sectional study of women reported 76 percent of HIV-positive and 42 percent of HIV-negative women had anal HPV DNA by PCR. Furthermore, 26 percent of 251 HIV-positive women were diagnosed with AIN compared with 8 percent of 68 HIV-negative women (Palefsky, 2000).

In general, lower genital tract disease risk factors in women with HIV were found to be similar to those for CIN. Risks included a CD4+ count less than 200 cells/ÂµL and the presence of HPV DNA (Jamieson, 2006). Similarly in these women, studies report that decreasing CD4+ and increasing viral load counts also correlate with the detection and increased prevalence and persistence of HPV infection (Palefsky, 1999; Strickler, 2005).

Cervical Cytology Screening

It is unclear whether the degree of immunosuppression in women with HIV infection correlates with the progression of abnormal cervical cytology. Specifically, investigations suggest that high viral loads may result in escalated cytologic abnormalities. Cardillo and colleagues (2001) recently examined the association between cervicovaginal Pap smears from HIV-positive women and their CD4+ counts and HIV viral load. This review of 108 HIV-positive women found the degree of immunosuppression may contribute to the development of intraepithelial lesions (Cardillo, 2001). In addition, higher rates of CIN postconization recurrence have been observed among HIV-positive women, and those who showed a recurrence of dysplasia were more likely to have failed highly active anti-retroviral therapy (HAART) than those without recurrence (Gilles, 2005).

Decreased Pap smear sensitivity or specificity has not been demonstrated between HIV-positive and HIV-negative women (Spinillo, 1998). Because HIV infection is linked to a significantly higher risk of developing squamous intraepithelial lesions, cervicovaginal cytologic screening should be obtained every six months for the first year after an HIV infection diagnosis (Byrne, 1989). With normal cytology, annual screening for life is recommended. In addition to vigilant cervical cytologic testing, women with HIV may benefit from routine anal Pap screens to monitor for AIN (Palefsky, 2001).

Abnormal Cytology Management

Any cytologic abnormality is an indication for colposcopic evaluation. This includes atypical squamous cells of undetermined significance (ASC-US), the mildest cytologic abnormality defined in the Bethesda nomenclature system. In a study of women with ASC-US, Wright and co-workers (1996) reported that HIV-positive women were twice as likely to have underlying dysplasia compared with HIV-negative women. Given the increased frequency of cytologic abnormalities and the increased possibility for underlying dysplasia with a single ASC-US Pap smear, HIV-positive women require colposcopic evaluation of any atypical cells. HIV-positive women with dysplasia of the cervix are often found to have extensive dysplastic epithelial disease throughout the lower genital tract including the vagina, vulva, and anus (Hillemanns, 1996). Therefore, any abnormal cytology warrants colposcopy of the entire lower genital tract.

Treatment

Ablative therapy is not recommended for HIV-positive women with biopsy proven lower genital tract disease. Excisional procedures including loop electrosurgical excision procedure (LEEP), carbon dioxide laser, or cold-knife conization provide histologic margins for evaluation. Although excisional therapy is effective for eradicating CIN in immunocompetent patients, the same treatment seems to be effective only in preventing progression to cancer in HIV-infected women (Heard, 2005). Moreover, recurrence rates for excised lower genital tract disease are higher in women with HIV compared with those without HIV infection.

Effects of Highly Active Anti-Retroviral Therapy

Because of effective highly active anti-retroviral therapy (HAART), AIDS patients are living longer and expressing greater life satisfaction. However, the therapeutic impact of HAART on HPV infection is poorly understood and conflicting results have been reported (Heard, 2004). Cervical HPV and CIN are increased in HIV-positive women compared with risk-matched HIV-negative controls, and HAART appears to have only limited ability to eradicate HPV infection and induce regression of CIN (Palefsky, 2003). Immune restoration with HAART is insufficient to clear HPV as persistent HPV DNA remains detectable in most patients taking HAART (Heard, 2004). Moreover, multiple studies report a 62 to 73 percent recurrence rate for CIN after removal of the squamocolumnar junction in HIV-positive women despite HAART (Holcomb, 1999; Tate, 2002). However, Heard and colleagues

(2005) found this antiviral agent may have a strong positive impact on the recurrence rate of CIN after surgery and may delay the recurrence of HPV-related disease.

To date, HAART has not been shown to consistently improve the natural history of HPV-related diseases. Indeed, if HAART leads to increased longevity yet does not alter the incidence or progression of HPV-related disease, individuals on HAART may have sufficient time to develop HPV-related epithelial cancers (de SanjosÃ©, 2002).

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Clinical Pearl

7/17/2007: MCINDOE VAGINOPLASTY FOR NEOVAGINA CREATION

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Introduction

Creation of a functional vagina is the treatment goal for many women with congenital agenesis of the vagina. Although several surgical and nonsurgical approaches have been used, the McIndoe procedure is the most commonly employed in the United States. With this technique, a canal is formed between the urethra and urinary bladder anteriorly and the rectum posteriorly (McIndoe, 1938). A skin graft obtained from the patientâ€™s buttock, thigh, or inguinal regional is then wrapped around a soft mold and placed into the newly created vagina to allow epithelialization. Alternatively, other materials have been used to line the neovagina and include amnionic membrane, cutaneous and myocutaneous flaps, buccal mucosa, and Interceed absorbable adhesion barrier (Ethicon, Somerville, NJ) (Ashworth, 1986; Lin, 2003; Motoyama, 2003; McCraw, 1976).

Preoperative Considerations

Patient Selection. Vaginal stricture can be a significant complication following the McIndoe procedure (Alessandrescu, 1996). Thus, adherence to a postoperative regimen of vaginal dilatation is mandatory. For this reason, surgery may be postponed until the patient has reached a level of maturity to comply (American College of Obstetricians and Gynecologists, 2002).

Consent. Prior to surgery, patients should be informed of overall success rates with this procedure. In the Mayo Clinic series of 225 patients, the McIndoe procedure provided a functional vagina to afford â€œsatisfactoryâ€• intercourse in 85 percent of patients. In this review, the cumulative complication rate was 10 percent and included vaginal stricture, pelvic organ prolapse, graft failure, postcoital bleeding, and fistulas involving either the bladder or rectum (Klingele, 2003). Additionally, complications at the skin graft harvest site involved cheloid formation, wound infection, and postoperative dysaesthesias.

Patient Preparation. Intravenous administration of a second-generation cephalosporin such as cefoxitin 2g in a single preoperative dose is recommended. Bowel preparation is completed the evening prior to surgery.

Intraoperative Considerations

INSTRUMENTS

Electrodermatome. The skin grafts used to line the neovagina are harvested from the donor site with the aid of an electrodermatome, which is able to shave grafts of varying size and depth. Both split-thickness and full-thickness skin grafts have been used in the McIndoe procedure, and the electrodermatome settings are adjusted to shave the desired depth.

Vaginal Mold. Following graft harvesting and neovagina formation, a stent is needed to apply the graft to the vaginal walls and hold it in place. Both soft and rigid forms have been used. Rigid mold materials have included balsa wood, pyrex, plastic, and synthetic silicone-based materials (McIndoe, 1938; Ozek, 1999; Seccia, 2002; Yu, 2004). Unfortunately, rigid or semi-rigid stents have led to graft loss, fibrosis, contracture, and pressure-related bladder or rectal fistulas. Use of soft stents has decreased the number of these complications. Inflatable rubber stents or condoms filled with foam rubber or other soft compressible materials are examples (Adamson, 2004; Barutcu, 1998; Concannon, 1993). The vagina graft produces abundant exudates and poor drainage may lead to graft maceration, sloughing, and graft detachment. Accordingly, suction has been attached to the soft stents to aid drainage of the neovagina (Yu, 2004).

Postoperative Considerations

A soft stent and Foley catheter are left in place for 7 days following surgery. To minimize dislodgement of the mold and wound contamination, a low-residue diet and loperamide, 2 mg bid orally, is used to limit defecation.

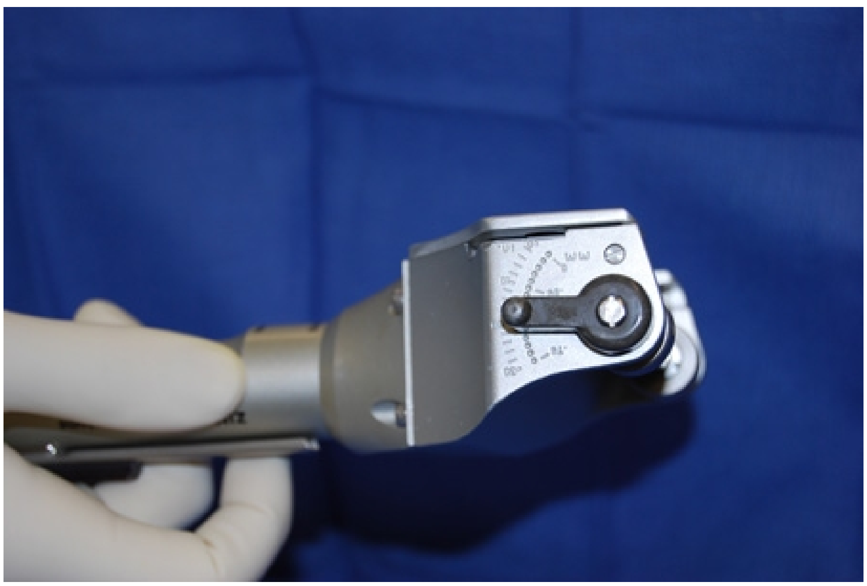
At the time of mold removal, an operating room, general anesthesia, and dorsal lithotomy position are employed. Stitches in the labia minora are cut and the mold is removed. To lessen the risk of graft avulsion, irrigation is used to reduce adherence between graft and stent. Commonly the size of the mold placed at surgery is too large for maintenance use. Therefore a smaller mold may initially be used and then gradually replaced with larger ones as the vagina stretches.

Several schedules for postoperative dilatation have been described. For the first 6 weeks following surgery, the dilator is worn continuously except during defecation. During the subsequent 6 weeks, it is used only at night. Following these initial 3 months, patients are then instructed to either wear the dilator at night or engage in intercourse twice each week.

General anesthesia is administered and the patient is positioned supine for skin graft harvesting from the thigh. Alternatively, the graft may be taken from the buttock, hip, or inguinal area. Goals of harvesting are to choose a location which has minimal hair growth and is cosmetically discreet. The assistance of a plastic surgeon may be enlisted for skin graft procurement.

The surgeon first marks the outline of the wound on the skin of the donor site, enlarging it by 3 to 5 percent to allow for skin shrinkage immediately after excision.

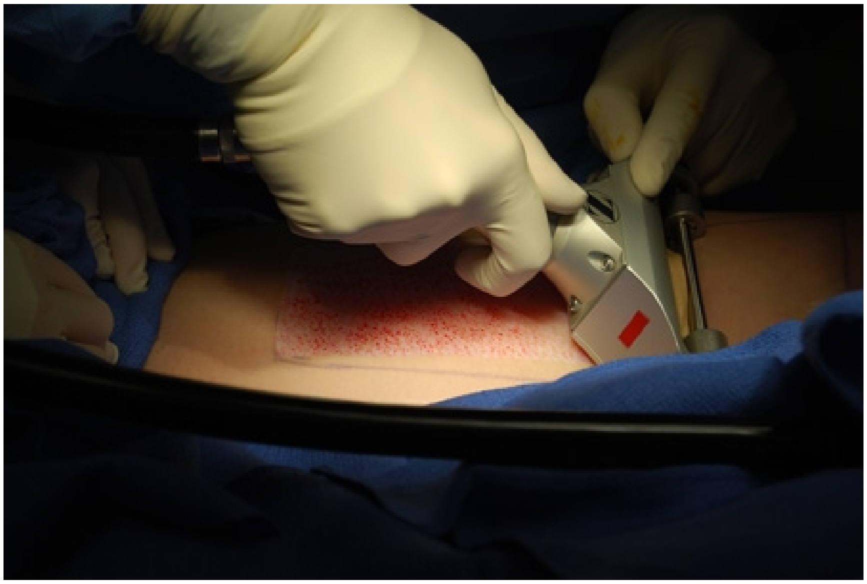
Electrodermatome.



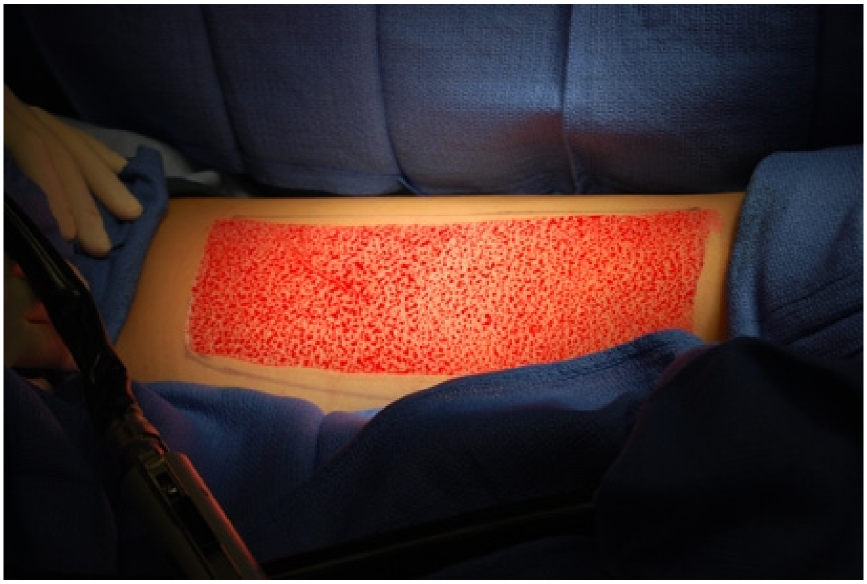
Graft thickness is preselected.

The surgeon uses the electrodermatome to remove a single strip of skin that is typically 0.018 inch thick, 8 to 9 cm wide, and 18 to 20 cm long. Alternatively, 2 smaller strips of 5 cm by 10 cm can be obtained from each buttock.

The graft is collected in front of the electrodermatome.

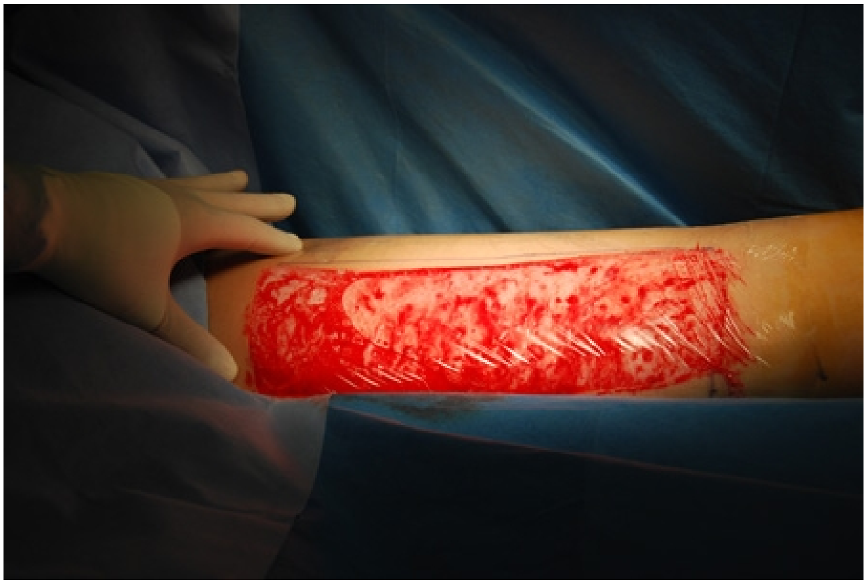


The graft is removed from the dermatome.



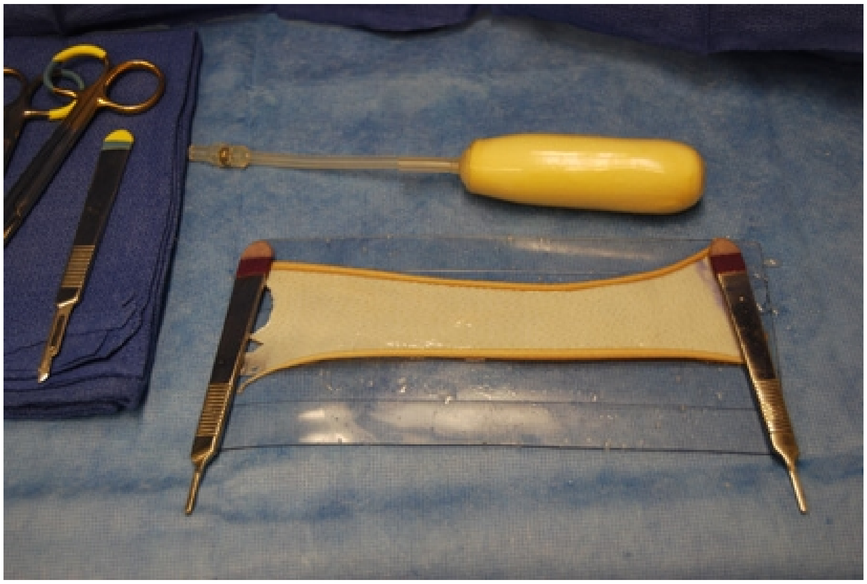
Graft harvest site immediately after harvesting.

Harvest site wound care.



The harvest site is dressed with a Tegaderm dressing.

Following excision, the graft is placed in a pan of sterile saline.



This picture displays the unrolled graft (below) and the soft mold (above). Note the suction tubing leaving the end of the soft mold. Adequate drainage of excess fluid from beneath the graft and from the vagina prevents tissue maceration and improves graft adherence.

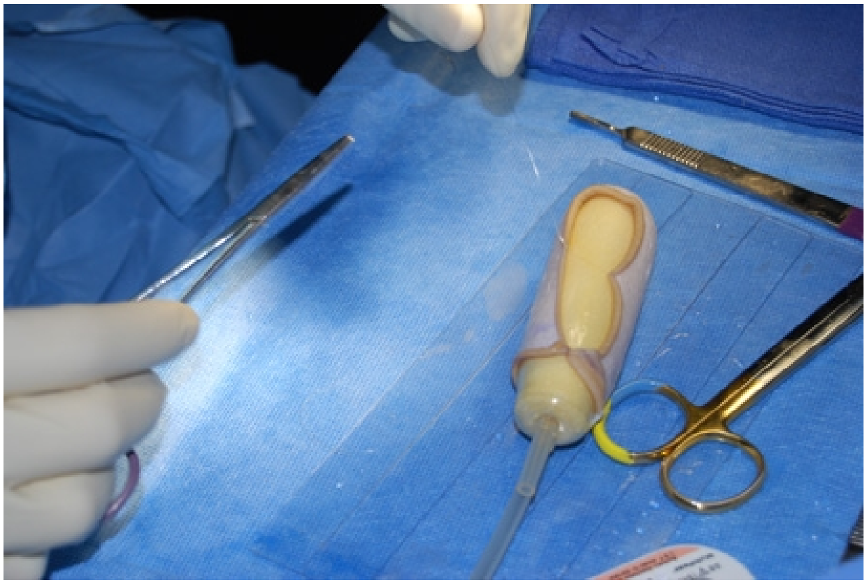
The graft is scored to allow drainage once in place. Elimination of excess fluid from beneath the graft promotes its adherence to the vaginal walls.

One end of the graft is placed at the base of the mold, and the graft is then draped up and over the mold tip.

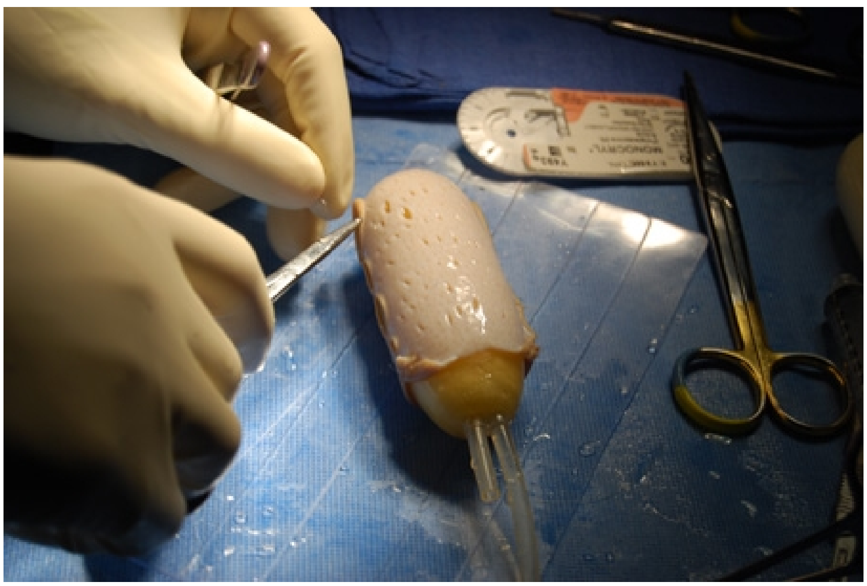
The external surface of the skin faces the mold.

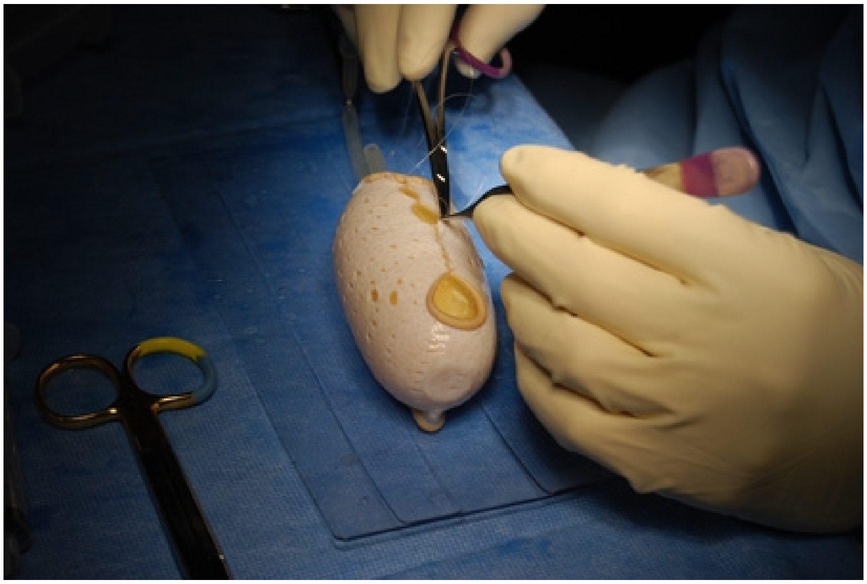
Skin graft in place around mold. Note drainage tube.

The lateral edges of the skin graft are then approximated on either side of the mold using interrupted sutures.



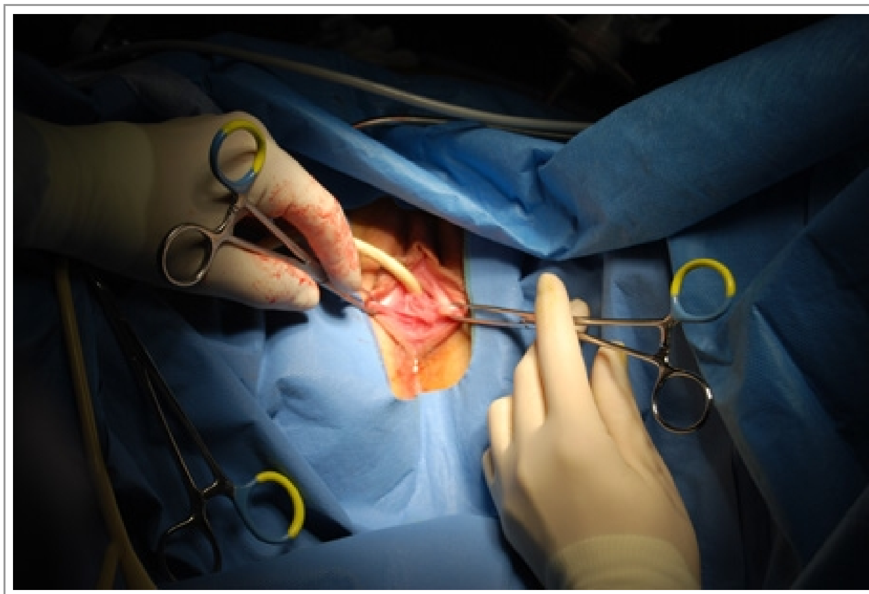
Continued suturing.



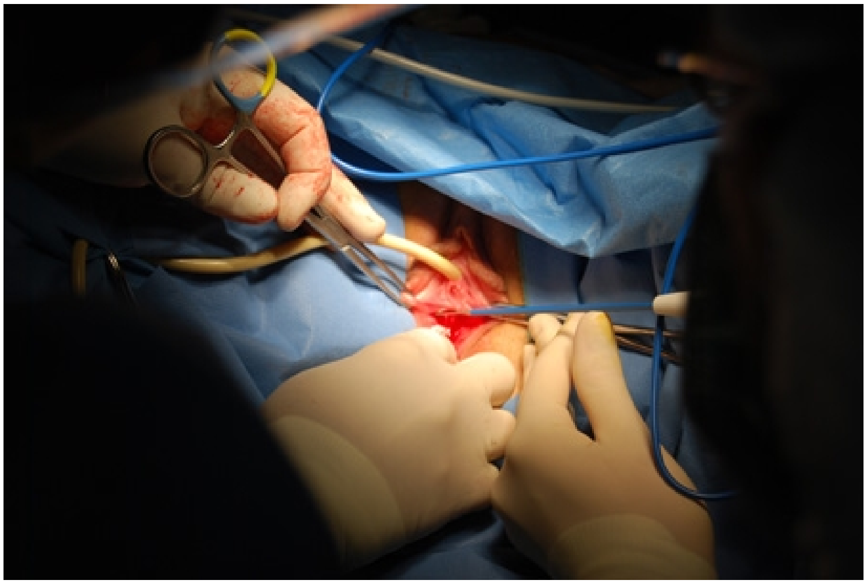


Graft sutured in place around the soft mold.

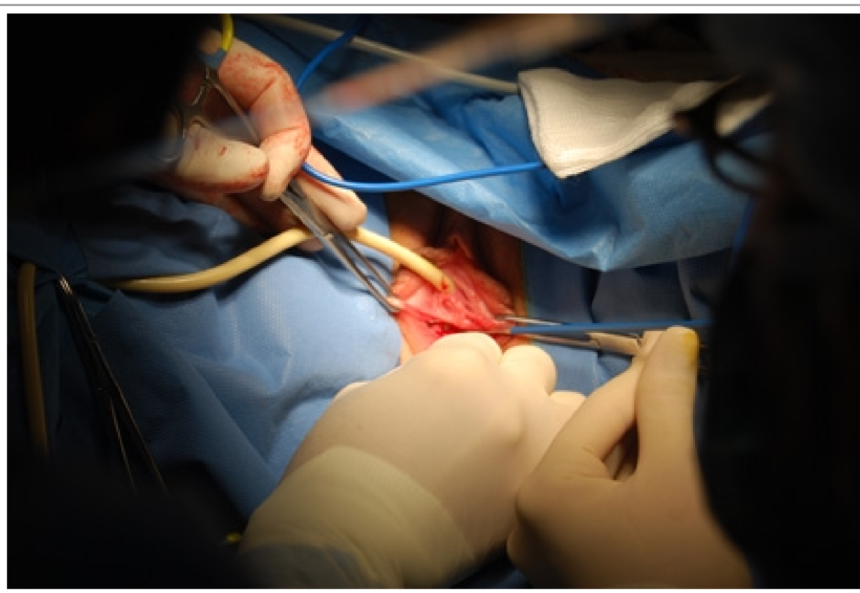
Concurrently with creation of the vaginal mold, the patient is placed in dorsal lithotomy position. Perineal cleansing is performed, and a Foley catheter placed. A dimple in the vestibule is typically identified below the urethra.



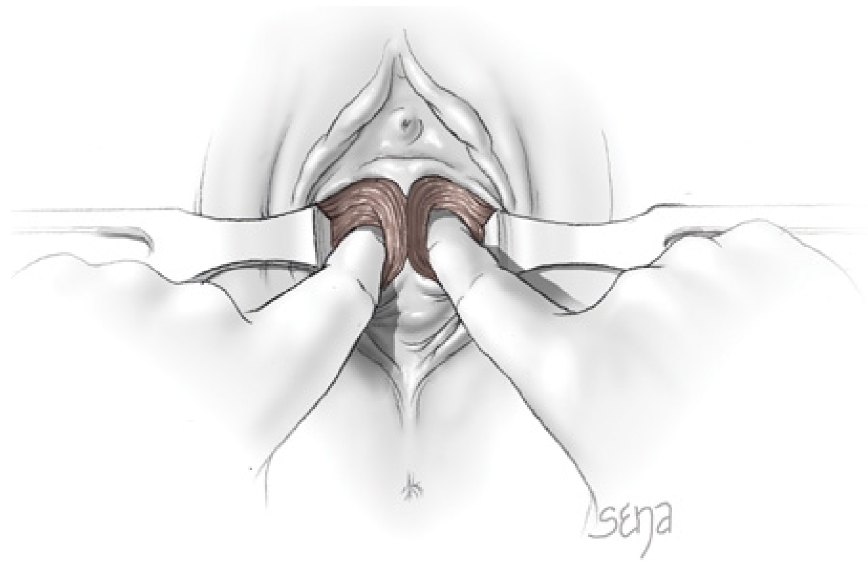
The lower edge of each labia minora is grasped with Allis clamps and extended laterally.



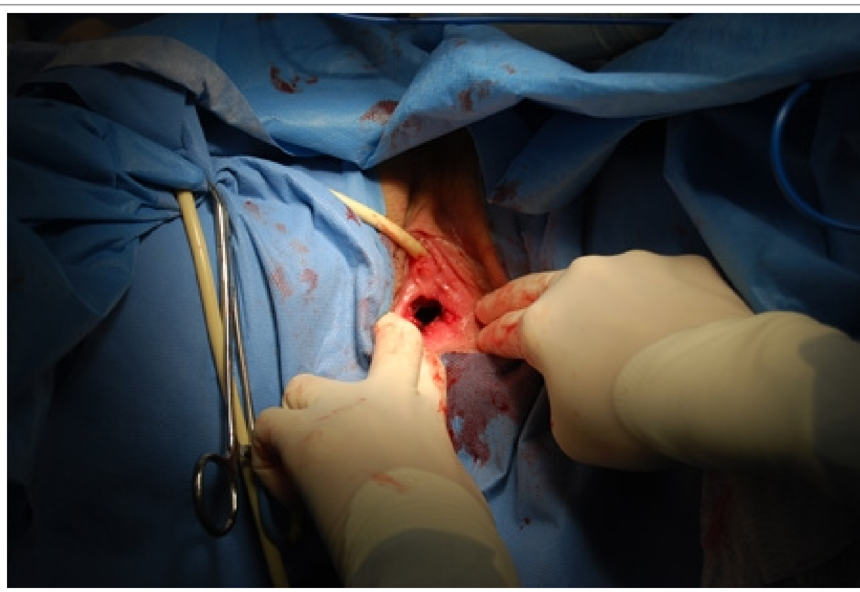
A 2 to 3 cm transverse incision is sharply made across it the dimple. In creation of the new vagina, the goal is to create a canal that is bounded anteriorly by the fascia that supports the urethra and bladder. Posterior limits involve the perirectal fascia and rectum. Lateral borders are the puborectalis muscles. Vaginal depth approximates 12 cm, but entering the cul-de-sac of Douglas peritoneum should be avoided. Thus, the canal is extended to within 2 cm of the cul-de-sac of Douglas. This leaves a layer of connective tissue affixed to the peritoneum. First, the skin graft will attach more effectively to this connective tissue than to the smooth peritoneal surface. Secondly, rates of subsequent enterocoele formation are lowered.



During dissection, several points are noteworthy. First, with initial caudal dissection, the surgeon may meet greater resistance than with the tissues more cephalad. Additionally during dissection, a finger may be placed by the surgeon into the rectum to identify its location and avert perforation. Similarly, the Foley catheter may serve as an orientation tool anteriorly.

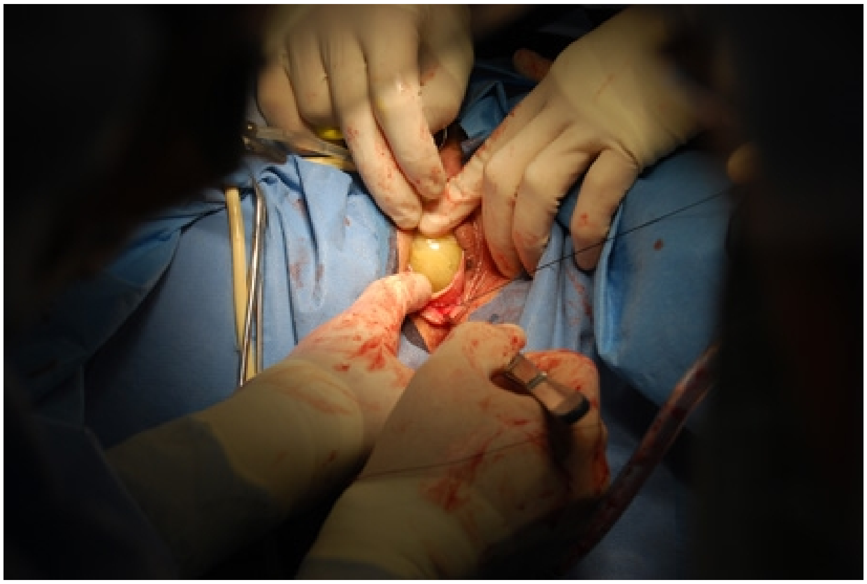


Following the initial incision, two canals are created on either side of the median raphe, which is a midline collection of dense connective tissue bands that stretch between the urethra and bladder above and the rectum below. These canals are initially formed using a spreading motion with blunt-tipped scissors. Fingers are then insinuated into the forming canals. Pressure is exerted cephalad to extend the canal depth. Additionally, the finger pads are rolled outward and lateral pressure is applied to widen the canal. Posterior pressure should be avoided to prevent entering the rectum.

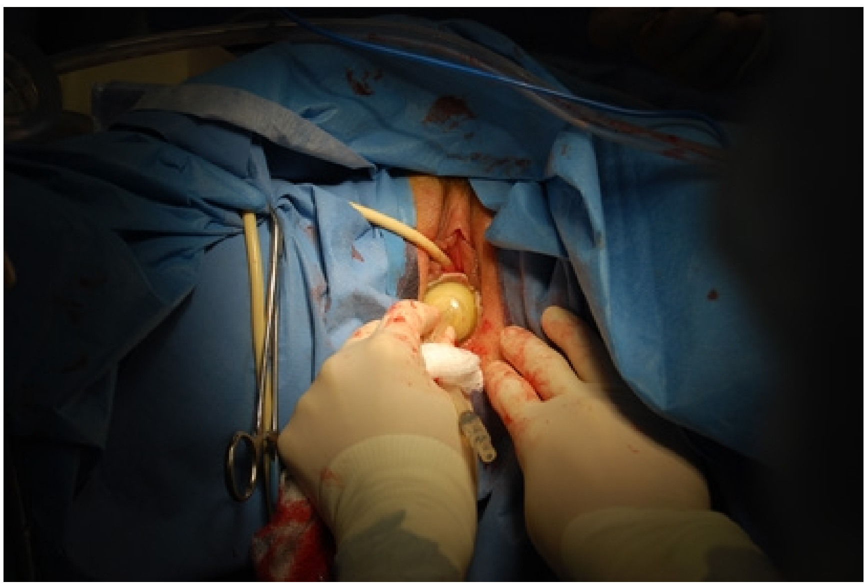


Upon completion of the two smaller canals, the median raphe is cut. The final single canal measures approximately 10 to 12 cm deep and 3 fingerbreadths wide.

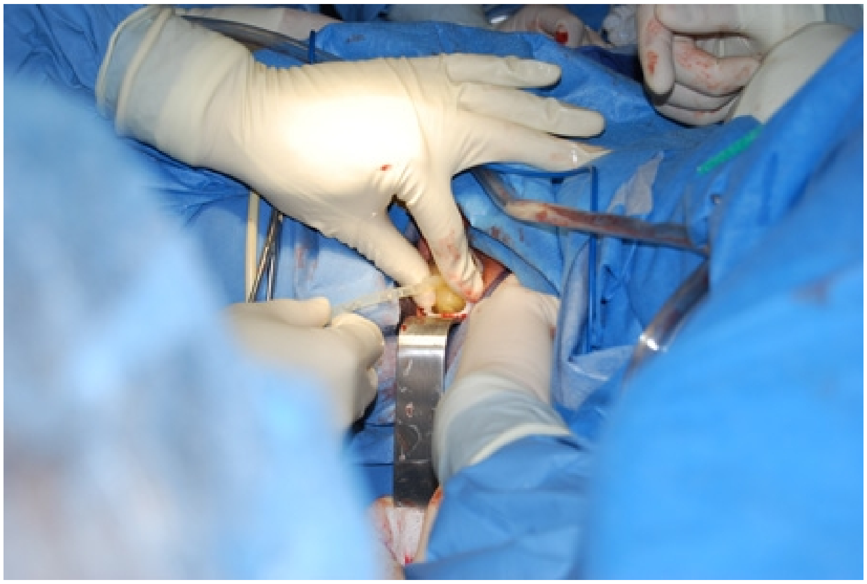
Collections of blood can separate the mold from the canal bed, thus hemostasis is required prior to mold insertion.



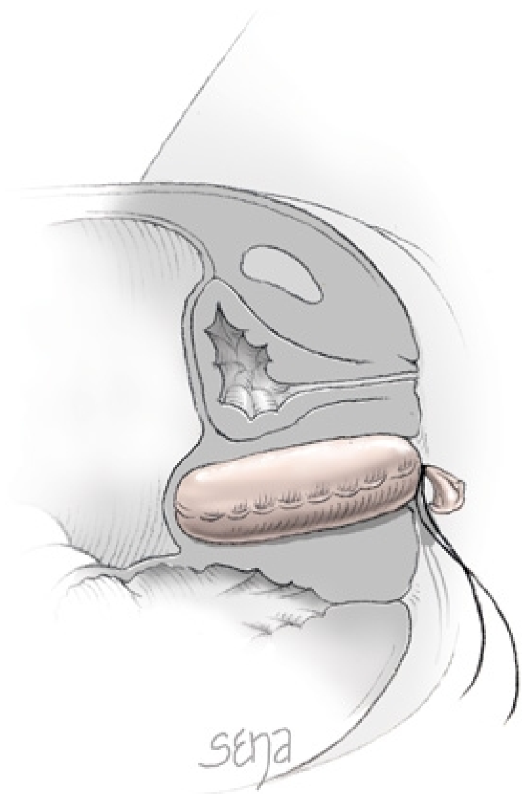
Once appropriately sized and constructed, the mold is then inserted.



Customizing the mold to the size of the created neovaginal canal is essential. If a mold width is too large, it can cause pressure necrosis or inhibit adequate drainage, which as noted earlier can lead to tissue maceration. Moreover, at the time of postoperative mold removal a mold which is too large and snuggly fitted into the neovagina may pull loose the graft.



Soft mold and graft in place.



Lateral image depicting the soft mold in place.

Edges of the skin graft at the distal end of the mold are then reapproximated to the distal opening of the neovagina using 4- or 5-0 delayed absorbable suture. The labia minora, if sufficiently long, can be sutured together along the midline with 2-0 silk sutures to help hold the mold in place for the first 7 postoperative days. An elastic compression dressing is placed on the perineum.

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MEDICAL HISTORY AND PHYSICAL EXAMINATION

For many women, gynecologists often serve as both specialist and primary care provider, and as such, are given an opportunity to prevent and treat a wide variety of diseases. The incidence of these may vary greatly depending on the age group treated. Thus, the focus of medical questioning should reflect these changing risks.

Following historical inventory, a complete physical examination is completed (American College of Obstetricians and Gynecologists, 2003c). Many women present to their gynecologists with complaints specific to the breast, vulva, or vagina. Accordingly, these are often areas of increased focus, and their evaluation is described below.

Breast Examination

Although mammography has been shown to effectively detect breast cancers, clinical breast examination (CBE) may identify a small portion of these malignancies not detected with mammography. Additionally, CBE may identify cancer in young women, who are not typical candidates for mammography (McDonald, 2004). Clinical breast examination can be completed with various methods. However, in an attempt to standardize performance, a committee for the American Cancer Society has described a CBE that combines visual inspection with axillary and breast palpation (Saslow, 2004).

BREAST INSPECTION

Initially, the breasts should be viewed as a woman sits on the table's edge with her hands pushing against her hips to flex the pectoralis muscles. Alone, this position enhances asymmetry, and additional arm positions, such as placing arms above the head, are not required to add vital information. Breast skin is inspected for erythema; retraction; scaling, especially over the nipple; and edema, termed *peau d'orange* change. Additionally, the breasts and axillae are observed for contour symmetry.

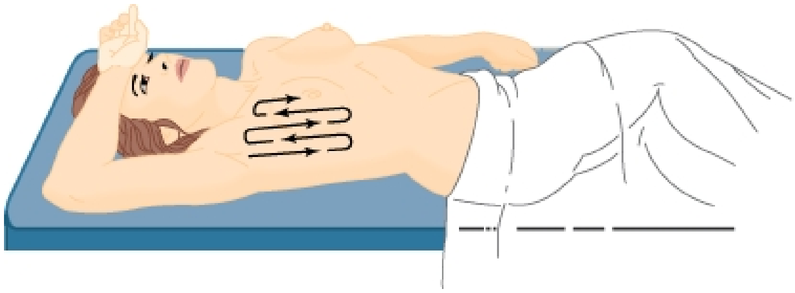
LYMPH NODE EVALUATION

Following inspection, axillary, supraclavicular, and infraclavicular lymph nodes are palpated most easily with a woman seated and her arm resting at her side but supported by the examiner. The axilla is bounded by the pectoralis major muscle ventrally and the latissimus dorsi muscle dorsally. Lymph nodes are detected as the examiner's hand glides from high to low in the axilla and momentarily compresses nodes against the lateral chest wall. In a thin patient, one or more mobile lymph nodes measuring <1 cm in diameter are commonly appreciated. The first lymph node to become involved with breast cancer metastases (the sentinel node) is nearly always located just behind the midportion of the pectoralis major muscle.

BREAST PALPATION

After inspection, breast palpation is completed with a woman supine and with one hand above her head to stretch breast tissue across the chest wall (Fig. 1-1). Examination should include breast tissue bounded by the clavicle, sternal border, inframammary crease, and midaxillary line. Breast palpation within this bounded area is approached in a linear fashion. The technique should use the finger pads in a continuous rolling, gliding circular motion (Fig. 1-2). At each palpation point, tissues should be assessed both superficially and deeply (Fig. 1-3). During CBE, intentional attempts at nipple discharge expression are not required unless a *spontaneous* discharge has been described by the patient.

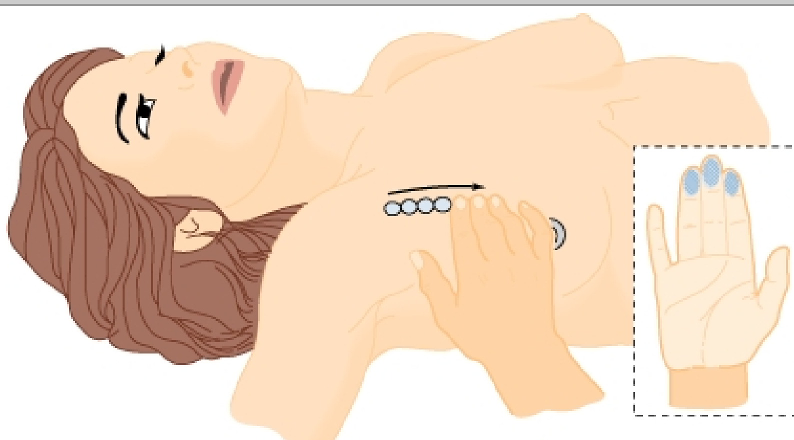
FIGURE 1-1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Image depicting recommended patient positioning and direction of palpation during clinical breast examination. *(From Barton, 1999, with permission.)*

FIGURE 1-2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Image depicting the recommended palpation technique, which uses the finger pads and a circular rolling motion. *(From Barton, 1999, with permission.)*

FIGURE 1-3

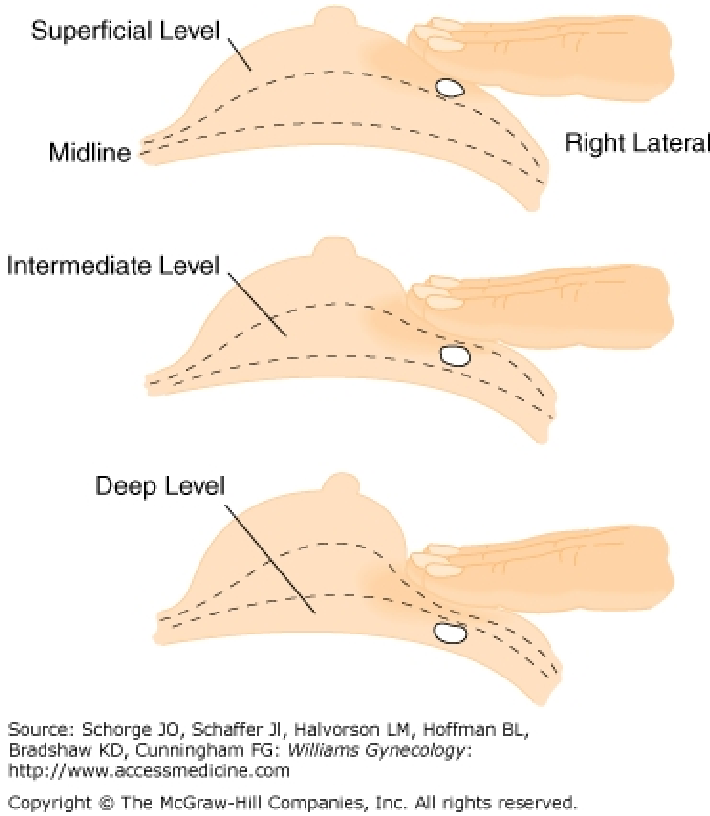


Image depicting palpation through several depths at each point along the linear path. *(From Barton, 1999, with permission.)*

If abnormal breast findings are noted, they are described by their location in the right or left breast, clock position, distance from the areola, and size. Evaluation and treatment of breast and nipple diseases are described more fully in Chapter 12.

Pelvic Examination

This examination is typically performed with a patient supine, legs in dorsal lithotomy position, and feet resting in stirrups. The head of the bed is elevated 30Â° to relax abdominal wall muscles for bimanual examination. A woman should be assured that she may stop or pause the examination at any time. Moreover, each part of the evaluation should be announced or described before its performance.

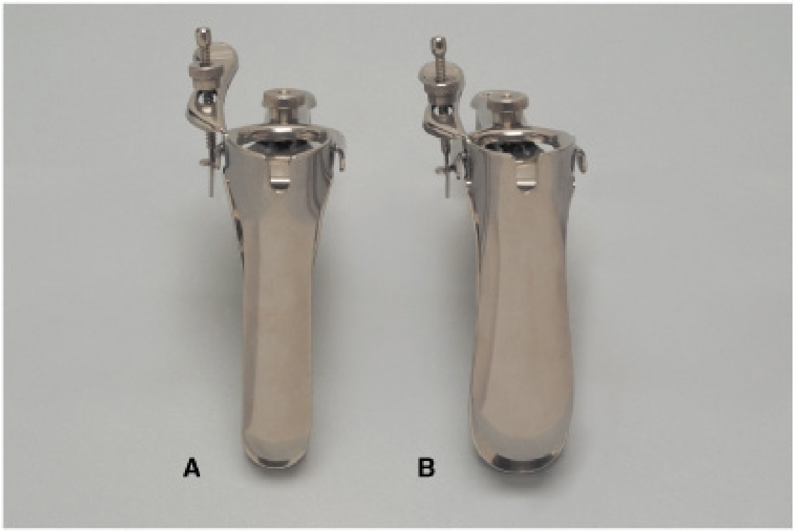
INGUINAL LYMPH NODES AND PERINEAL INSPECTION

Pelvic cancers and infections may drain to the inguinal lymph nodes, and these should be palpated during examination. Following this, a methodical inspection of the perineum should extend from the mons ventrally, to the genitocrural folds laterally, and to the anus. Infections and neoplasms that involve the vulva may also involve perianal skin, and this area should be similarly inspected. Some clinicians also palpate for Bartholin and paraurethral gland pathology. However, in most cases, patient symptoms and asymmetry in these areas will dictate the need for their evaluation.

SPECULUM EXAMINATION

The vagina and cervix are typically viewed after placement of either a Graves or Pederson speculum (Fig. 1-4). Within these two general classes of speculums, various sizes are available to accommodate vaginal length and laxity. Prior to insertion, a speculum may be warmed. Additionally, lubrication may add comfort to insertion. Griffith and colleagues (2005) found that water-based gel lubricants, placed on the outer speculum bill, did not increase unsatisfactory conventional Pap smear cytology or decrease Chlamydia trachomatis detection rates compared with water lubrication.

FIGURE 1-4



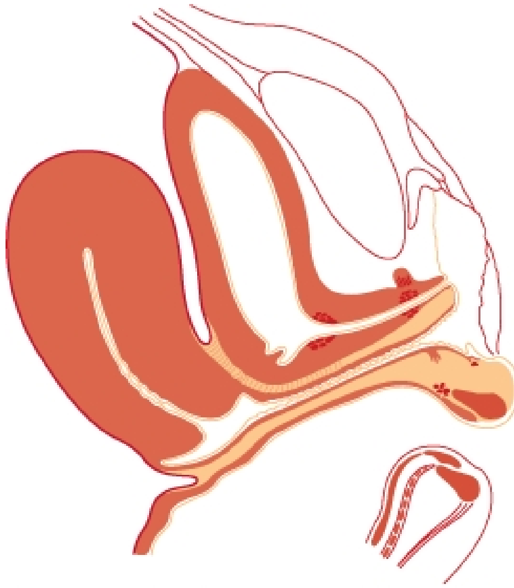
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photograph displays Pederson **(A)** and Graves **(B)** vaginal speculums. *(Courtesy of Dave Gresham.)*

Prior to insertion, the labia minora are gently separated, and the urethra is identified. Because of urethral sensitivity, the speculum is inserted below the meatus. Alternatively, prior to speculum placement, an index finger may be placed in the vagina and pressure placed against the bulbocavernosus muscle. A woman is then encouraged to relax this posterior wall muscle to improve comfort with speculum insertion. This practice may prove especially helpful for women undergoing their first examination, those with infrequent coitus, or those with heightened anxiety.

With speculum insertion, the vagina commonly contracts, and a woman may note pressure or discomfort. A pause at this point typically is followed by vaginal muscle relaxation. As the speculum bill is completely inserted, it is angled 30Â° downward to reach most cervices. Commonly, the uterus lies in an anteverted position, and the face of the cervix lies against the posterior vaginal wall (Fig. 1-5).

FIGURE 1-5



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Image depicting an anteverted uterus. Note that the ectocervix faces the posterior vaginal wall. *(From Reiffenstuhl and Platzer, 1975, with permission.)*

As the speculum is opened, the ectocervix can be identified. Vaginal walls and cervix should be inspected for masses, ulceration, or unusual discharge. As outlined in Chapter 29, Performing a Pap Test, a Pap smear is obtained and additional swabs for culture or microscopic evaluation may also be collected (see Chap. 3, Diagnosis).

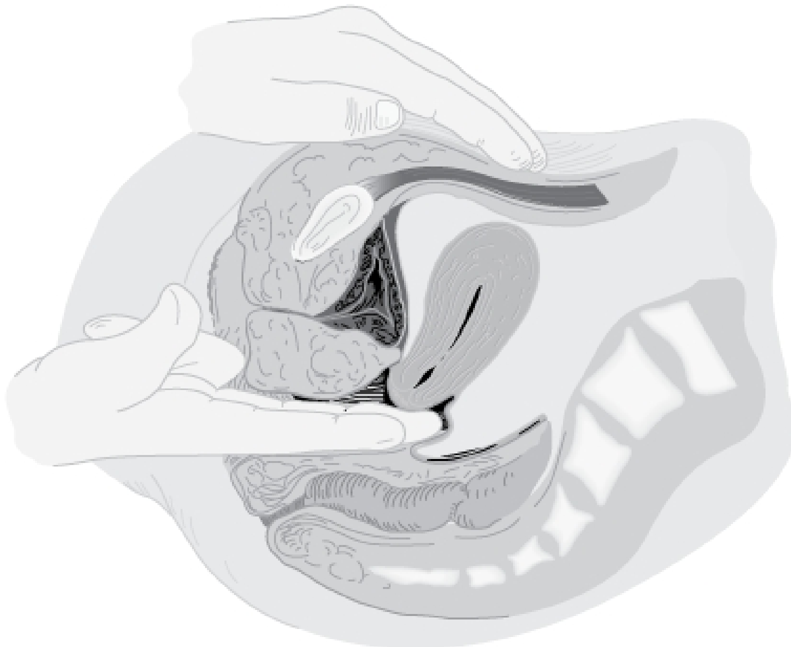
BIMANUAL EXAMINATION

Uterine and adnexal size, mobility, and tenderness can be assessed during bimanual examination. For women with prior hysterectomy and adnexectomy, bimanual examination is still valuable and can be used to exclude other pelvic pathology.

During this examination, a gloved index and middle finger are inserted together into the vagina until the cervix is reached. To ease insertion, a water-based lubricant may be initially applied to these fingers. Once the cervix is reached, uterine orientation can be quickly assessed by sweeping the index finger inward along the anterior surface of the cervix. In those with an anteverted position, the uterine isthmus is noted to sweep upward, whereas in those with a retroverted position, a soft bladder is palpated. However, in those with a retroverted uterus, if a finger is swept along the cervix's posterior surface, the isthmus is felt to sweep downward. With a retroverted uterus, this same finger is continued posteriorly to the fundus and then side-to-side to assess uterine size and tenderness.

To determine the size of an anteverted uterus, fingers are placed beneath the cervix, and upward pressure tilts the fundus toward the anterior abdominal wall. A clinician's opposite hand is placed against the abdominal wall to locate the upward fundal pressure (Fig. 1-6).

FIGURE 1-6



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Image depicting bimanual examination of an anteverted uterus. *(From Hacker, 1998, with permission.)*

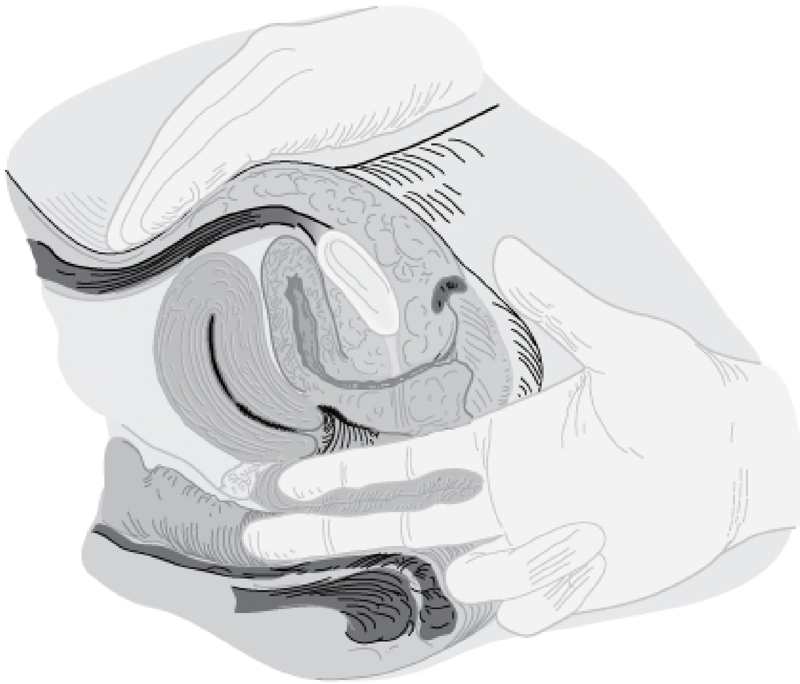
To assess adnexa, clinicians use their two vaginal fingers to lift adnexa from the cul-de-sac toward the anterior abdominal wall. An adnexum is trapped between these vaginal fingers and the clinician's other hand, which is exerting downward pressure against the lower abdomen. For those with normal-sized uteri, this abdominal hand is typically best placed just above each inguinal ligament and pubic rami.

RECTOVAGINAL EXAMINATION

The decision to perform a rectovaginal examination varies among providers. Although some prefer to complete this evaluation on all adults, others elect to perform rectovaginal examination for those with specific indications such as pelvic pain, an identified pelvic mass, rectal symptoms, or need for colon cancer screening.

Gloves may be changed between bimanual and rectovaginal examinations to avoid contamination of the rectum with potential vaginal pathogens. Initially, an index finger is placed into the vagina and a middle finger into the rectum. These fingers are swept horizontally against one another in a scissoring fashion to assess the rectovaginal septum for scarring or peritoneal studding (Fig. 1-7). The index finger is removed, and the middle finger completes a circular sweep of the rectal vault to exclude masses. If immediate guaiac testing is indicated, it may be performed with a sample from this portion of the examination.

FIGURE 1-7



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Image depicting rectovaginal examination. *(From Hacker, 1998, with permission.)*

PREVENTIVE CARE

As primary care providers, gynecologists have an opportunity to prevent leading causes of female morbidity and mortality. Accordingly, a familiarity with screening and general treatment guidelines is essential.

Infection Prevention

VACCINATION

Although many vaccines are recommended routinely for most adults, others may be warranted less frequently and are indicated because of co-morbid patient risks. Recommendations for adult vaccination are summarized in Table 1-1, and a complete discussion of specific as well as general guidelines can be found at the Centers for Disease Control and Prevention (CDC) website: http://www.cdc.gov/vaccines/recs/schedules/downloads/adult/06-07/adult-schedule.pdf .

Table 1-1 Summary of Recommendations for Adult Immunization

Vaccine Name and Route	**Reason to Vaccinate**	**Vaccine Administration (any vaccine can be given with another)**	**Contraindications and Precautions[a] (mild illness is not a contraindication)**
Influenza Trivalent inactivated influenza vaccine (TIV) *Give IM*	■ Persons aged 50 yrs and older ■ Persons with serious medical problems such as heart disease, diabetes, renal dysfunction, and conditions that compromise respiratory function	■ October and November are ideal months to give TIV ■ LAIV may be given as early as August	**Precaution** ■ History of Guillain-BarrÃ© syndrome within 6 wks previous TIV

	respiratory function. ■ Women who will be pregnant during the influenza season (December-March) ■ Persons working or living with at-risk people ■ Household contacts or caregivers of children 0-59 mos ■ Travelers to at-risk areas. ■ Students or other persons in institutional settings ■ Anyone wishing to reduce the risk of influenza	■ May continue to give TIV and LAIV from December through March	
Influenza Live attenuated influenza vaccine (LAIV) *Give intranasally*	■ Healthy, nonpregnant persons aged 49 yrs and younger who meet any of the last 5 conditions for TIV	■ October and November are ideal months to give TIV ■ LAIV may be given as early as August ■ May continue to give TIV and LAIV from December through March	**Contraindication** ■ As above, plus pregnancy or serious chronic medical disorders
Pneumococcal polysaccharide (PPV) *Give IM or SC*	■ Persons aged 65 yrs and older ■ Persons who have chronic illness, asplenia, or immunosuppression	■ Routinely given as a onetime dose; administer if previous vaccination history is unknown ■ One-time revaccination is recommended 5 yrs later for persons at highest risk and for persons age 65 yrs and older if the 1st dose was given prior to age 65 and 5 yrs have elapsed since the previous dose	
Hepatitis B (Hep B) *Give IM*	■ All adolescents; any adult wishing to obtain immunity. ■ High-risk persons, including household contacts and partners of HBsAg-positive persons; injecting drug users; heterosexuals with more than one	■ Three doses are needed on a 0-, 1-, 6-mo schedule ■ Alternative timing options for vaccination include 0, 2, 4 mos and 0, 1, 4 mos. If the	

	sex partner; MSM; persons with STDs; patients receiving hemodialysis; recipients of certain blood products; health care workers, and certain international travelers. ▪ Persons with chronic liver disease	series is delayed between doses, do not restart series, but complete it ▪ For the hepatitis A and B combination vaccine, three doses are needed on a 0-, 1-, 6-mo schedule. Recipients must be 18 yrs or older	
Hepatitis A (Hep A) *Give IM*	▪ Persons who travel or work anywhere except the U.S., Western Europe, New Zealand, Australia, Canada, and Japan ▪ Persons with chronic liver disease; drug users; MSM; people with clotting-factor disorders; and food handlers when health authorities or private employers determine vaccination to be cost effective ▪ Anyone wishing to obtain immunity to hepatitis A	▪ Two doses are needed. ▪ The minimum interval between doses #1 and #2 is 6 mos	**Precaution** ▪ Safety during pregnancy has not been determined, so benefits should be weighed against potential risk
Td, Tdap (Tetanus, diphtheria, pertussis) *Give IM*	▪ All adults who lack a history of primary series consisting of at least three doses of tetanus-and diphtheria-containing vaccine ▪ A booster dose of tetanus- and diphtheria-containing toxoid may be needed for wound management as early as 5 yrs after receiving a previous dose *For Tdap (tetanus- and diphtheria-toxoids with acellular pertussis vaccine) only:* ▪ All adults aged younger than 65 yrs who have not received Tdap	▪ For persons who are unvaccinated, complete the primary series with Td (spaced at 0, 1- to 2-mo, and 6- to 12-mo intervals). One dose of Tdap may be used for any dose if aged 19-64 yrs ▪ Give Td booster every 10 yrs after the primary series has been completed. For adults aged 19-64 yrs, a 1-time dose of Tdap is recommended to replace the text Td	**Contraindication** ▪ For Tdap only, history of encephalopathy within 7 days following DTP/DTaP **Precaution** ▪ Guillain-BarrÃ© syndrome within 6 wks of receiving a previous dose of tetanus toxoid-containing vaccine ▪ Unstable neurologic condition **Note** : Use of Td or Tdap is not contraindicated in pregnancy. At the provider's discretion, either vaccine may be administered during the second or third trimester
Varicella (Var) (Chickenpox) *Give SC*	▪ All adults without evidence of immunity, which is defined as a history of vaccination, previously	▪ Two doses are needed on a 0 and 1- or 2-mo schedule. If the second	**Contraindications** ▪ Pregnancy or possibility of pregnancy within 4 wks

	diagnosed varicella disease, or laboratory evidence of immunity	dose is delayed, do not repeat dose #1; just give dose #2	■ Immunocompromised persons
Meningococcal Conjugate vaccine (MCV4) *Give IM* Polysaccharide vaccine (MPSV4) *Give SC*	■ College freshmen living in dormitories ■ Anatomic or function asplenia or terminal complement component deficiencies ■ Travel to or residence in countries in which meningococcal disease is hyperendemic or epidemic	■ One dose is needed ■ If previous vaccine was MPSV4, revaccinate after 5 yrs if risk continues ■ Revaccination after MCV4 is not recommended	**Precaution** ■ For MCV4 only, history of Guillain- BarrÃ© syndrome
MMR (Measles, mumps, rubella) *Give SC*	■ Persons born in 1957 or later should receive at least one dose of MMR if there is no serologic proof of immunity ■ Women of childbearing age who do not have acceptable evidence of rubella immunity or vaccination	■ One or two doses are needed ■ If a pregnant woman is found to be rubella susceptible, administer MMR postpartum	**Contraindications** ■ Pregnancy or possibility of pregnancy within 4 wks **Precaution** ■ Severe immunosuppression ■ History of thrombocytopenia or thrombocytopenia purpura
Human papillomavirus (HPV) *Give IM*	■ All previously unvaccinated women through age 26 yrs	■ Three doses are needed on a 0, 1- to 2- , and 6-mo schedule	**Precaution** ■ Data on vaccination in pregnancy are limited; therefore, vaccination should be delayed until postpartum

[a] Previous anaphylactic reaction to any of a vaccine's components serves as a contraindication for any vaccine. Moderate to severe illness is a precaution to vaccination.

DTP = diphtheria, tetanus, pertussis vaccine; HBSAg = hepatitis B surface antigen; MSM = men having sex with men; STD = sexually transmitted disease.

Modified from Immunization Action Coalition, 2006, with permission.

SEXUALLY TRANSMITTED DISEASE SCREENING

Routine screening for sexually transmitted disease is not warranted for all women. However, certain testing is recommended for selected groups to decrease morbidity and disease transmission (Table 1-2). These and other infections of the reproductive tract are discussed in Chapter 3.

Table 1-2 Sexually Transmitted Disease Screening Guidelines for Nonpregnant, Sexually Active Asymptomatic Women		
Infectious Agent	**Recommendations**	**Risk Factors**
Chlamydia trachomatis + *Neisseria gonorrhoeae*	Screen all ≤25 years. Screen those older if risk factors present	New or multiple partners; inconsistent condom use; sex work; concurrent STD, prior chlamydial infection or gonorrhea
Treponema pallidum	Should screen those with risk factors	Sex work; confinement in adult correction facility; MSM
HIV virus	Should screen those with risk factors	Multiple partners; injection drug use; sex work; concurrent STD; MSM; transfusion between 1978 and 1985
Hepatitis C virus	May screen those with risk factors	Injection drug use; dialysis; partner with hepatitis C; multiple partners; received blood products prior to 1990
Hepatitis B virus	No routine screening	
Herpes simplex virus 2	No routine screening	

HIV = human immunodeficiency virus; MSM = men having sex with men; STD = sexually transmitted disease.

Contraception

For reproductive-aged women, contraceptive needs or plans for pregnancy should be discussed annually. Contraceptive counseling is covered in Chapter 5 but generally should include education on methods, their use, efficacy, side effects, noncontraceptive benefits, and contraindications. However, despite efforts to provide contraception, nearly half of all pregnancies are unintended. Accordingly, a discussion of emergency contraceptive methods is warranted. Additionally, all reproductive-aged women are encouraged to take a 400-μg folic acid supplement daily to prevent fetal neural-tube defects (NTDs) if pregnancy occurs. Women at higher risk for fetuses with NTD should supplement with 4 mg orally each day (American College of Obstetricians and Gynecologists, 2003b).

Alternatively, for those desiring pregnancy, topics found in Table 1-3 should be addressed to maximize maternal and fetal health (American College of Obstetricians and Gynecologists, 2005).

Table 1-3 Preconception Topics	
Action	**Risk Reduction**
Review contraceptive use	Prevent unintended pregnancy
Advise smoking cessation or at minimum, decreased smoking	Decrease risk of pregnancy loss Increase birthweight Decrease risk of sudden infant death syndrome
Advise abstinence from alcohol or at minimum, decreased consumption	Prevent fetal alcohol syndrome
Supplement with folic acid	Decrease risk of neuralâ€"tube defects
Screen for HIV infection	Decrease perinatal transmission by giving antiretroviral treatment Avoid transmission via breast milk
Screen for hepatitis B virus	Protect neonate from infection by administering vaccine antepartum
Screen for other sexually transmissible infections	Protect maternal fertility Prevent fetal and neonatal infection
Immunize	Prevent vaccine-preventable diseases
Control diabetes	Decrease risk of congenital anomaliesxs
Screen for genetic diseases	Provide choices about pregnancy outcome
Counsel about domestic violence	Prevent injuries
Review psychosocial status	Improve emotional support and well-being

HIV = human immunodeficiency virus.

Modified from Hatcher, 2004, with permission.

Cancer Screening

For women having periodic health examinations, screening for certain cancers may be indicated for early detection.

CERVICAL CANCER

This cancer is common and is preventable in many cases with routine Pap smear screening. A detailed discussion of Pap smear collection technique and guidelines is presented in Chapter 29, Performing a Pap Test, but a brief overview is provided here.

In general, women should begin Pap smear screening within 3 years after beginning vaginal intercourse and no later than age 21. Subsequently, regular Pap test collection should follow every year or every 2 years using newer liquid-based Pap tests (American College of Obstetricians and Gynecologists, 2003a; Saslow, 2002). In those older than 30, if three normal test results are obtained, then screening may be spaced at 2- to 3-year intervals. However, co-morbid risks for cervical cancer such as diethylstilbestrol (DES) exposure and immunosuppression may warrant annual screening even in this age group (see Chap. 29, Screening Recommendations) (Smith, 2006).

In contrast, screening may be discontinued for selected groups. For example, women aged 70 years or older who have had three consecutive normal Pap test results, no history of preinvasive lesions, and no co-morbid risks for cervical cancer may elect to halt screening. In addition, following hysterectomy, women without a history of invasive or preinvasive cervical disease may also choose to stop cytologic screening (U.S. Preventive Services Task Force, 2003a).

ENDOMETRIAL CANCER

Some women with multiple family members with colon cancer may have hereditary nonpolyposis colon cancer (HNPCC), as defined in Chapter 33. For women with HNPCC or those at high risk for this syndrome, annual screening should be offered for endometrial cancer with endometrial biopsy beginning at age 35 (American Cancer Society, 2006b).

For most other asymptomatic women, routine endometrial cancer screening is not recommended. However, clinicians should educate women, especially those with risk factors, about this cancer's typical symptoms.

OVARIAN CANCER

Routine screening of asymptomatic women at low risk for ovarian cancer with either cancer antigen 125 (CA125) level measurement or sonography is not recommended. Currently, annual pelvic examination is the primary prevention tool for these women. However, for women who carry BRCA1 or BRCA2 gene mutations or those with a strong family history of breast and ovarian cancer, these two screening tools may be offered. A complete discussion of ovarian cancer screening can be found in Chapter 35, Genetic Screening.

BREAST CANCER

Guidelines from the American Cancer Society were published in 2003 (Table 1-4). Based on trials showing decreased mortality in women 40 years and older who were screened with mammography, mammograms are recommended starting at age 40 for those with average risk and may be continued yearly (Smith, 2003). For those with greater risk, early or more frequent screening or the addition of other imaging tools may be warranted. A fuller discussion of breast cancer and screening can be found in Chapter 12, Breast Cancer Screening.

Table 1-4 American Cancer Society Guidelines for Early Breast Cancer Detection

Women at Average Risk	Begin mammography at age 40.
	For women in their 20s and 30s, it is recommended that CBE be part of a periodic health examination, preferably at least every 3 years. Asymptomatic women aged 40 and older should continue to receive CBE as part of a periodic health examination, preferably annually.
	Beginning in their 20s, women should be told about the benefits and limitations of BSE. Women who choose to do BSE should receive instruction at their periodic health examination. It is acceptable for women to choose not to do BSE or to do BSE irregularly.
Older Women	Screening decisions in older women should be individualized in the context of current health status. As long as a woman would be a candidate for treatment, she should continue to be screened with mammography.
Women at Increased Risk	Women at increased risk of breast cancer might benefit from additional screening strategies. These may include earlier initiation of screening, shorter screening intervals, or the addition of screening modalities such as ultrasonography or magnetic resonance imaging.

BSE = breast self-examination; CBE = clinical breast examination.

Abbreviated from Smith, 2003, with permission.

COLON CANCER

Several organizations recommend screening patients at average risk for colorectal cancer beginning at age 50 with any of the five

methods shown in Table 1-5. Prior to fecal occult blood testing (FOBT), women should avoid nonsteroidal anti-inflammatory drugs (NSAIDs) 7 days prior to testing. Additionally, vitamin C, red meats, raw cauliflower, broccoli, members of the radish family, and melons should be avoided for 3 days before testing. Positive tests warrant further evaluation with colonoscopy.

Table 1-5 Summary of Recommendations for Colorectal Cancer Screening in Average-Risk Patients[a]

	U.S. Preventive Services Task Force	**American College of Gastroenterology**	**American Cancer Society**
FOBT	Good evidence for periodic testing	Annual	Annual
FS	Fair evidence for periodic testing	Every 5 years	Every 5 years
FS + FOBT	Fair evidence for periodic testing	Annual, every 5 years, respectively	Annual, every 5 years, respectively
Colonoscopy	No direct evidence of CRC mortality reduction; indirect evidence supports its use	Every 10 years	Every 10 years
DCBE	No direct evidence of CRC mortality reduction	Every 5 years	Every 5 years

[a] Screening begins at age 50 for those at average risk.

CRC = colorectal cancer; DCBE = double-contrast barium enema; FOBT = fecal occult blood testing; FS = flexible sigmoidoscopy.

Modified from Huang, 2005, with permission.

Although these guidelines are appropriate for those with average risk, individuals with a personal or family history of colon cancer, chronic inflammatory bowel disease, prior polyps, or other high-risk factors should be screened more frequently (American Cancer Society, 2006a).

Osteoporosis

In the United States, approximately 15 percent of women older than 50 years have osteoporosis, and 35 to 50 percent have osteopenia (Ettinger, 2003). These bone-weakening conditions lead to increased rates of fracture, and bone mass density has been shown to correlate inversely with risks for these fractures. Accordingly, tools that measure bone density such as dual-energy x-ray absorptiometry (DEXA) scanning are used to identify bone loss and predict fracture risk (see Chap. 21, Diagnosis of Osteoporosis). Screening guidelines from the National Osteoporosis Foundation (2003) as to the appropriate use of such radiologic tools is listed in Table 1-6.

Table 1-6 General Guidelines for Prevention and Treatment of Osteoporosis
Counsel all women on the risk of osteoporosis and related fractures.
Advise all women to consume adequate amounts of calcium (at least 1,200 mg/d, including supplements if necessary) and vitamin D (400 to 800 IU/d for those at risk of deficiency).
Recommend regular weight-bearing and muscle-strengthening exercise.
Advise women to avoid smoking and excessive alcohol intake.
Recommend BMD testing to all women aged 65 yrs and older.
Recommend BMD testing to younger postmenopausal women who have one or more risk factors (other than being white, postmenopausal, and female) (See Table 21-6).
Recommend BMD testing to women who have suffered a fragility fracture.
Initiate therapy to reduce fracture risk in postmenopausal women with BMD T-scores by central dual-energy x-ray absorptiometry (DEXA) below â€“2 in the absence of risk factors and in women with T-scores below â€“1.5 if one or more risk factors is present.
Consider postmenopausal women with vertebral or hip fractures candidates for osteoporosis treatment.
Current pharmacologic options for osteoporosis prevention and/or treatment are bisphosphonates (alendronate and risedronate), calcitonin, estrogens and/or hormone therapy, parathyroid hormone, and raloxifene.

BMD = bone mineral density.

From National Osteoporosis Foundation, 2003, with permission.

Obesity

DIAGNOSIS AND RISKS

In 2003, 62 percent of women in the U.S. were considered overweight or obese (Ogden, 2006). *Overweight* is defined as a body mass index (BMI) ranging from 25 to 29.9 kg/m^2 , whereas *obesity* describes individuals with BMIs, greater than 30 kg/m^2 . *Normal weight* falls within BMIs of 18.5 and 24.9 (Table 1-7). In addition to BMI, waist circumference positively correlates with abdominal fat content, which if increased, can serve as a separate co-morbid risk. For women, waist circumferences greater than 88 cm (35 inches) are considered increased (National Heart, Lung, and Blood Institute, 2000). Circumference is measured at the level of the iliac crests at the end of normal expiration. The measuring tape should be snug but not indent the skin.

Table 1-7 Body Mass Index Tables

BMI	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
Height (inches)	**Body Weight (pounds)**																
58	91	96	100	105	110	115	119	124	129	134	138	143	148	153	158	162	167
59	94	99	104	109	114	119	124	128	133	138	143	148	153	158	163	168	173
60	97	102	107	112	118	123	128	133	138	143	148	153	158	163	168	174	179
61	100	106	111	116	122	127	132	137	143	148	153	158	164	169	174	180	185
62	104	109	115	120	126	131	136	142	147	153	158	164	169	175	180	186	191
63	107	113	118	124	130	135	141	146	152	158	163	169	175	180	186	191	197
64	110	116	122	128	134	140	145	151	157	163	169	174	180	186	192	197	204
65	114	120	126	132	138	144	150	156	162	168	174	180	186	192	198	204	210
66	118	124	130	136	142	148	155	161	167	173	179	186	192	198	204	210	216
67	121	127	134	140	146	153	159	166	172	178	185	191	198	204	211	217	223
68	125	131	138	144	151	158	164	171	177	184	190	197	203	210	216	223	230
69	128	135	142	149	155	162	169	176	182	189	196	203	209	216	223	230	236
70	132	139	146	153	160	167	174	181	188	195	202	209	216	222	229	236	243
71	136	143	150	157	165	172	179	186	193	200	208	215	222	229	236	243	250
72	140	147	154	162	169	177	184	191	199	206	213	221	228	235	242	250	258
73	144	151	159	166	174	182	189	197	204	212	219	227	235	242	250	257	265
74	148	155	163	171	179	186	194	202	210	218	225	233	241	249	256	264	272
75	152	160	168	176	184	192	200	208	216	224	232	240	248	256	264	272	279
76	156	164	172	180	189	197	205	213	221	230	238	246	254	263	271	279	287

BMI	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54
Height (inches)	**Body Weight (pounds)**																		
58	172	177	181	186	191	196	201	205	210	215	220	224	229	234	239	244	248	253	258
59	178	183	188	193	198	203	208	212	217	222	227	232	237	242	247	252	257	262	267
60	184	189	194	199	204	209	215	220	225	230	235	240	245	250	255	261	266	271	276
61	190	195	201	206	211	217	222	227	232	238	243	248	254	259	264	269	275	280	285
62	196	202	207	213	218	224	229	235	240	246	251	256	262	267	273	278	284	289	295
63	203	208	214	220	225	231	237	242	248	254	259	265	270	278	282	287	293	299	304
64	209	215	221	227	232	238	244	250	256	262	267	273	279	285	291	296	302	308	314
65	216	222	228	234	240	246	252	258	264	270	276	282	288	294	300	306	312	318	324
66	223	229	235	241	247	253	260	266	272	278	284	291	297	303	309	315	322	328	334
67	230	236	242	249	255	261	268	274	280	287	293	299	306	312	319	325	331	338	344
68	236	243	249	256	262	269	276	282	289	295	302	308	315	322	328	335	341	348	354
69	243	250	257	263	270	277	284	291	297	304	311	318	324	331	338	345	351	358	365
70	250	257	264	271	278	285	292	299	306	313	320	327	334	341	348	355	362	369	376
71	257	265	272	279	286	293	301	308	315	322	329	338	343	351	358	365	372	379	386
72	265	272	279	287	294	302	309	316	324	331	338	346	353	361	368	375	383	390	397
73	272	280	288	295	302	310	318	325	333	340	348	355	363	371	378	386	393	401	408
74	280	287	295	303	311	319	326	334	342	350	358	365	373	381	389	396	404	412	420
75	287	295	303	311	319	327	335	343	351	359	367	375	383	391	399	407	415	423	431
76	295	304	312	320	328	336	344	353	361	369	377	385	394	402	410	418	426	435	443

In addition to the social stigma that often accompanies increased body weight, overweight and obese women are at increased risk for developing hypertension, hypercholesterolemia, type 2 diabetes mellitus, gallbladder disease, knee osteoarthritis, sleep apnea, coronary heart disease (CHD), and certain cancers (Must, 1999; National Task Force on the Prevention and Treatment of Obesity, 2000). Accordingly, treatment of these women is often directed toward weight loss as well as management of other co-morbid risk factors (Table 1-8).

Table 1-8 Obesity Co-Morbid Risk Factors
Established coronary heart disease
Other concurrent atherosclerotic disease
Peripheral vascular disease
Abdominal aortic aneurysm
Symptomatic coronary artery disease
Type 2 diabetes mellitus
Sleep apnea
Cigarette smoking
Chronic hypertension
Abnormal lipid levels
Elevated LDL cholesterol levels
Elevated triglyceride levels
Decreased HDL cholesterol levels
Family history of early CHD
Gynecologic abnormalities
Menorrhagia or metrorrhagia
Endometrial hyperplasia
Endometrial cancer
Osteoarthritis
Gallstones

CHD = coronary heart disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

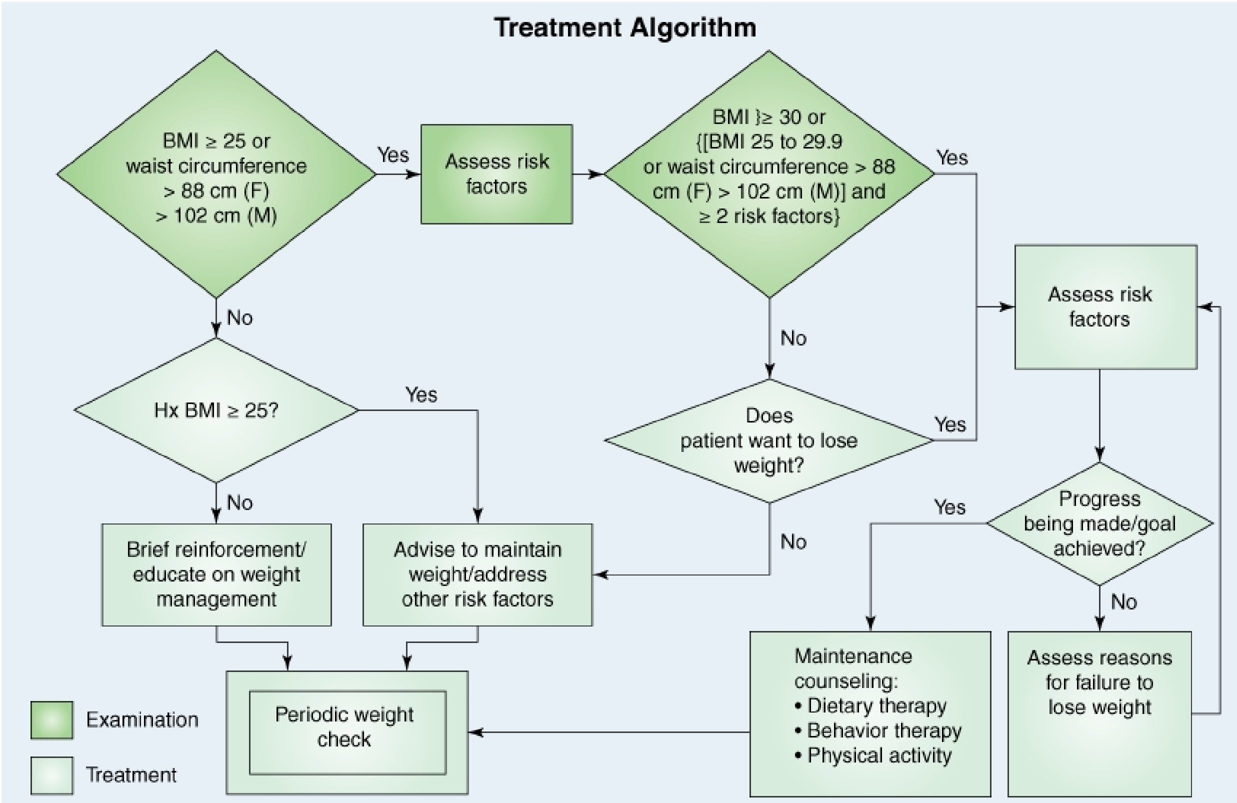
Compiled from National Heart, Lung, and Blood Institute, 2000, with permission.

TREATMENT

Lifestyle Changes

As seen in Fig. 1-8, for overweight women, if two or more risks are present or if an increased waist circumference is present, then management should focus on moderate weight loss through diet and exercise. For obese women, more substantial weight loss over a prolonged period should be promoted with an initial goal of a 10-percent weight loss over 6 months. A detailed discussion of dietary weight loss extends beyond this chapter's scope, but several clinician and patient aids can be found at: http://www.nhlbi.nih.gov/guidelines/obesity/prctgd_c.pdf .

FIGURE 1-8



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Algorithm for the diagnosis and management of overweight and obese individuals. *(From National Heart, Lung, Blood Institute, 2000.)*

In general, a 10-percent loss within 6 months can be reached in those with BMIs from 27 to 35 with a daily 300- to 500-kcal intake reduction. In those with higher BMIs, a similar loss can be achieved following a 500- to 1,000-kcal reduction.

Medications

In addition to diet and exercise, pharmacologic or surgical options may be implemented for selected obese patients. Sibutramine (Meridia, Abbott Laboratories, North Chicago, IL) is a centrally acting monoamine-reuptake inhibitor that primarily acts as an appetite suppressant (McNeely, 1998). Orlistat (Xenical, Roche Pharmaceutical, Nutley, NJ) is the other Food and Drug Administration (FDA)-approved agent for obesity. A reversible inhibitor of gastric and pancreatic lipases, orlistat leads to a 30-percent blockage of dietary fat absorption (Henness, 2006). The newest weight loss drug, approved in Europe and under consideration in the U.S. is rimonabant, the first cannabinoid (CB_1) antagonist. Receptors of the endocannabinoid system are extensively expressed in the brain, including areas vital to the control of food intake. Rimonabant acts as an appetite suppressant (Padwal, 2007).

Bariatric Surgery

As another adjunct to diet and exercise, bariatric surgery may be selected for those with BMIs ≥ 40 or with BMIs ≥ 35 if other co-morbid conditions are present (Buchwald, 2005). Of available procedures, gastric banding and Roux-en-Y gastric bypass are the most commonly performed (Brethauer, 2006). Both surgeries lead to substantial weight loss in individuals with morbid obesity and have been linked with improved co-morbid risk factors and decreased mortality rates (Christou, 2004; Sjostrom, 2004). However, surgical complications can be serious and include pulmonary embolism, gastrointestinal leaks in staple or suture lines, stomal obstruction or stenosis, and bleeding (Steinbrook, 2004).

Chronic Hypertension

Chronic hypertension is common and an estimated 39 million American women are hypertensive (American Heart Association, 2005). The risk of hypertension increases with age, and more than 65 percent of those older than 60 have elevated blood pressures (Ong, 2007; Vasan, 2002). Hypertension is a significant health concern and increases risks of myocardial infarction, stroke, congestive heart failure, renal disease, and peripheral vascular disease. To minimize these effects, gynecologists should be familiar with criteria used to diagnose hypertension. Although many may choose to refer their patients for treatment of hypertension, gynecologists should be aware of target goals and long-term risks associated with this disease.

DIAGNOSIS

Physical Examination

Blood pressures should ideally be taken with a woman seated in a chair with the tested arm resting on a table. An appropriately sized cuff is selected, and the cuff bladder should be large enough to encircle at least 80 percent of the arm. Hypertension is diagnosed if readings are elevated on at least two separate office visits.

As seen in Table 1-9, a new category of hypertension was introduced in 2003 by the Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (National Heart, Lung, and Blood Institute, 2003). *Prehypertension* is diagnosed if readings range from 130-139/80-89 mm Hg. This range is important, as women with prehypertension are at significantly increased risk of developing hypertension later (Wang, 2004). Additionally, compared with normal blood pressure readings, prehypertension is associated with greater risks for cardiovascular disease (CVD) (Mainous, 2004).

Table 1-9 Classification and Treatment of Hypertension

Classification	**SBP (mm Hg)**		**DBP (mm Hg)**	**No Compelling Indication[a]**	**Those with a Compelling Indication[a]**
Normal	<120	**and**	<80	No antihypertensive drug	No antihypertensive drug
Prehypertension	120â€“139	**or**	80â€“90	No antihypertensive drug	Drugs for the compelling indication(s).
Stage 1 hypertension	140â€“159	**or**	90â€“99	Thiazide-type diuretics for most. May consider ACEIs, ARBs, BBs, CCBs, or combination	Drugs for the compelling indication(s). ACEIs, ARBs, BBs, CCBs as needed
Stage 2 hypertension	≧ 160	**or**	≧ 100	Two-drug combination for most, usually thiazide- type diuretic and ACEIs or BB or CCB	Drugs for the compelling indication(s). Add diuretics, ACEIs, ARBs, BBs, CCBs, as needed

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensinâ€“receptor blocker; BB = β -blocker; CCB = calcium-channel blocker; DBP = diastolic blood pressure; SBP = systolic blood pressure.

[a] Compelling indications include (1) congestive heart failure, (2) myocardial infarction, (3) diabetes, (4) chronic renal failure, (5) prior stroke. Lifestyle modifications are encouraged for all and include (1) weight reduction if overweight, (2) alcohol intake limitation, (3) increased aerobic physical activity (30â€“45 minutes daily), (4) sodium intake reduction (<2.34 g/d), (5) smoking cessation, and (6) Dietary Approaches to Stop Hypertension (DASH) diet (See Table 1â€“11).

From National Heart, Lung, and Blood Institute 2003, with permission.

If hypertension is diagnosed, further examination should exclude underlying causes of hypertension and resultant end-organ disease (Table 1-10). Accordingly, examination should include confirmation of comparable blood pressure in the contralateral arm; optic fundi examination; calculation of BMI and measurement of waist circumference; auscultation for carotid, abdominal, and femoral bruits; thyroid gland palpation; heart and lung auscultation; abdominal examination for renal enlargement and abnormal aortic pulsation; and inspection for edema and pulses.

Table 1-10 Identifiable Causes of Hypertension
Chronic renal disease
Chronic steroid therapy and Cushing syndrome
Coarctation of the aorta
Drug-induced or drug-related
Nonsteroidal anti-inflammatory drugs
Cocaine and amphetamines
Sympathomimetics (decongestants, anorectics)
Oral contraceptives
Adrenal steroids
Cyclosporine and tacrolimus
Erythropoietin
Licorice
Herbal medicines (ephedra, ma huang)
Pheochromocytoma
Primary aldosteronism
Renovascular disease
Sleep apnea
Thyroid or parathyroid disease

Laboratory Tests and Other Diagnostic Procedures

Routine laboratory tests recommended before initiating therapy include an electrocardiogram, urinalysis, blood glucose, hematocrit, lipid profile, and serum potassium and creatinine testing. A more extensive search for identifiable causes may not be generally indicated unless hypertension is not controlled with initial treatment (Chobanian, 2003).

TREATMENT

Lifestyle intervention provides an effective means to lower blood pressure and can be used to prevent and treat hypertension (Table 1-11). However, if blood pressure is significantly elevated, resistant to lifestyle changes alone, or if other co-morbid conditions exist, then pharmacologic treatment may be needed to decrease long-term complications. Medications used for treatment are numerous and an extensive listing can be found at: http://www.nhlbi.nih.gov/guidelines/hypertension/express.pdf .

Table 1-11 Management of Prehypertension			
Strategy	**Recommendation**	**Approximate SBP Reduction**	**Effect on Incidence or Prevalence of Hypertension**
DASH dietary pattern	4â€“5 fruits/day 4â€“5 vegetables/day 2â€“3 low-fat diary/day <25% fat	3.5 mm Hg	Decreased by 62% (prevalence)
Weight loss	Effective in lowering BP even without attaining normal BMI	1 mm Hg/kg of weight loss	Decreased by 42% (incidence)
Reduced sodium intake	<2,400 mg/day	2 mm Hg per 76-mmol/L-per-day decrease	Decreased by 38% (incidence)
Physical activity	Moderate exercise ≥30 minutes most days	3â€“4 mm Hg	N/A
Moderation of alcohol intake	≤2 oz/day (men); ≤1 oz/day (women)	3.5 mm Hg	N/A

BMI = body mass index; DASH = dietary approaches to stop hypertension; N/A indicates not available; SBP = systolic blood pressure.

From Svetkey, 2005, with permission.

Diabetes Mellitus

Diabetes is common and approximately 20 million adults in the U.S. are diabetic (National Institute of Diabetes and Digestive and Kidney Disease, 2005). The long-term consequences of this endocrine disorder are serious and include coronary heart disease, stroke, peripheral vascular disease, periodontal disease, nephropathy, neuropathy, and retinopathy.

SCREENING

Currently, the U.S. Preventive Services Task Force (2003b) concludes that there is insufficient evidence to recommend routine screening of asymptomatic adults for type 2 diabetes, unless hyperlipidemia or hypertension is co-existent. However, the American Diabetes Association (2004) recommends that screening be considered at 3-year intervals beginning at age 45, particularly in those with BMIs ≥25. Moreover, testing should be considered at a younger age or completed more often in those who are overweight and have one or more of the other risk factors shown in Table 1-12. Aside from screening, women with overt hyperglycemia symptoms such as polyuria, polydipsia, and blurred vision should undergo diagnostic testing for diabetes.

Table 1-12 Risk Factors for Type 2 Diabetes
Age ≥ 45 years
Overweight (BMI ≥ 25)
Family history of diabetes (affected parents or siblings)
Habitual physical inactivity
Race/ethnicity (African-, Hispanic-, Native-, and Asian-Americans, and Pacific Islanders)
Previously identified IFG or IGT
History of GDM or delivery of a baby weighing >9 lbs
Hypertension (≥140/90 mm Hg in adults)
HDL cholesterol ≤35 mg/dL and/or triglyceride level ≥250 mg/dL
Polycystic ovary syndrome
History of vascular disease

BMI = body mass index; GDM = gestation diabetes mellitus; HDL = high-density lipoprotein; IFG = impaired fasting glucose; IGT = impaired glucose tolerance.

From American Diabetes Association, 2004, with permission.

Diabetes may be diagnosed by different methods, which are shown in Table 1-13. Laboratory measurement of plasma glucose concentration is performed on venous samples, and the diagnostic criteria are based on the use of such methods. Elevated values, in the absence of unequivocal hyperglycemia, must be confirmed on a subsequent day by any of these three methods. In contrast, although hemoglobin A_{1c} measurement and capillary blood glucose testing using a blood glucometer are effective monitoring tools, they are not currently recommended for diagnostic use (American Diabetes Association, 2004).

Table 1-13 Diagnostic Criteria for Diabetes Mellitus
Symptoms of diabetes plus casual plasma glucose concentration ≥200 mg/dL (*casual* is defined as any time of day without regard to time since last meal). The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.
or
FPG ≥126 mg/dL. *Fasting* is defined as no caloric intake for at least 8 h.
or
2-h postload glucose ≥200 mg/dL during an OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

FPG = fasting plasma glucose; OGTT = oral glucose tolerance test; WHO = World Health Organization.

From American Diabetes Association, 2004, with permission.

TREATMENT

Delayed onset and slower progression of many diabetic complications has been shown to follow control of elevated blood glucose

levels (Cleary, 2006; Fioretto, 2006; Martin, 2006). Control can be achieved with diet modification alone or combined with oral hypoglycemic agents or injectable insulin. To lower diabetic morbidity, therapy goals include hemoglobin A_{1c} levels below 7 percent, blood pressure readings below 130/80 mm Hg, low-density lipoprotein (LDL) levels less than 100 mg/dL, weight loss, and smoking cessation (National Diabetes Education Program, 2004).

Cardiovascular Disease

In 2004, nearly 37 percent of the female population was affected by cardiovascular disease and 460,000 women died from its complications (American Heart Association, 2005). Guidelines for prevention encourage surveillance and initial assessment of a woman's risk for cardiovascular disease (CVD) (Mosca, 2004). At its simplest, a woman's risk is calculated by totaling points assigned for smoking, age, lipid levels, and hypertension. An online calculator can be found at: http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=prof . Termed the *Framingham 10-year CHD risk score* , point totals are broadly categorized into risk level as: high risk (>20-percent risk of CHD), intermediate (10 to 20 percent 10-year risk), and lower risk (<10 percent risk). Recommendations for prevention of CVD are listed in Table 1-14 and are stratified according to these risk levels.

Table 1-14 Recommendations for Prevention of Cardiovascular Disease (CVD) in Women

High Risk (>20 percent risk of CVD)	**Intermediate Risk (10 to 20 percent risk)**	**Lower Risk (<10 percent risk)**
Strength of recommendation [a]		
Smoking cessation Physical activity/cardiac rehabilitation Diet therapy Healthy weight Blood pressure control Cholesterol control/therapy Aspirin therapy β-blocker therapy ACE inhibitor therapy (or ARB therapy if indicated) Management of diabetes	Smoking cessation Physical activity Heart-healthy diet Healthy weight Blood pressure control Cholesterol control	Smoking cessation Physical activity Heart-healthy diet Healthy weight Treatment of individual CVD risk factors as indicated
Strength of recommendation [b]		
Evaluation/therapy for depression Omega-3 fatty acid supplementation Folic acid supplementation	Aspirin therapy	

ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensinâ€“receptor blocker.

[a] Consistent, good-quality evidence.

[b] Inconsistent or limited-quality evidence. From Hayes, 2006, with permission.

Metabolic Syndrome

DIAGNOSIS AND PREVALENCE

This syndrome is a clustering of major cardiovascular disease risk factors (Table 1-15). At present, a single unifying cause of the metabolic syndrome has not been identified, and it may be precipitated by multiple underlying risk factors. Of these, abdominal obesity and insulin resistance appear most important (Grundy, 2005). There is currently debate surrounding the concept of a metabolic syndrome. A statement from the American Diabetes Association describes the need for additional data to confirm the veracity of this constellation as a true "syndrome". Until that time, they caution the use of this label for patients (Kahn, 2005). However, the metabolic syndrome is recognized as a major health risk by the World Health Organization (WHO), American Heart Association, and U.S. National Cholesterol Education Program Panel (Despres, 2006; Grundy, 2006).

Table 1-15 Diagnostic Criteria for Metabolic Syndrome

Any 3 of 5 Criteria Constitute a Diagnosis of Metabolic Syndrome	Categorical Cut Points
Elevated waist circumference	≥102 cm (≥40 inches) in men
	≥88 cm (≥35 inches) in women
Elevated TG levels	≥150 mg/dL
	or
	Drug treatment for elevated TG levels[a]
Reduced HDL levels	<40 mg/dL in men
	<50 mg/dL in women
	or
	Drug treatment for reduced HDL levels[a]
Elevated BP	≥130 mm Hg systolic BP
	or
	≥85 mm Hg diastolic BP
	or
	Drug treatment for hypertension
Elevated fasting glucose levels	≥100 mg/dL
	or
	Drug treatment for elevated glucose levels

BP = blood pressure; HDL = high-density lipoprotein; TG = triglyceride.

[a] Fibrates and nicotinic acid are the most commonly used drugs for elevated TG and reduced HDL. Patients taking these drugs are presumed to have high TG and low HDL levels.

Modified from Grundy, 2005, with permission.

This syndrome is common, and approximately 20 to 25 percent of U.S. adults meet diagnostic criteria. Although the genders appear

equally affected, Mexican Americans show the highest prevalence, and incidence appears to increase in all ethnicities with age (Ford, 2002). The sequelae associated with metabolic syndrome are significant and include an increased risk of type 2 diabetes and mortality from coronary heart disease CVD, and all causes (Lorenzo, 2003; Malik, 2004; Sattar, 2003). Among those with metabolic syndrome, risks are further increased by cigarette smoking and elevated LDL cholesterol levels.

TREATMENT

Goals of clinical management include reducing risks for clinical atherosclerotic disease and for type 2 diabetes mellitus. Accordingly, primary therapy for metabolic syndrome focuses on lifestyle modification, particularly weight reduction and increased exercise. During evaluation, each metabolic syndrome component should be addressed and treated in accordance with current guidelines. Moreover, drug therapy should follow current guidelines for treatment of each individual component (Eberly, 2006; Grundy, 2006; National Cholesterol Education Program, 2001).

Dyslipidemia

HYPERCHOLESTEROLEMIA

Screening and Diagnosis

Data support that low-density lipoprotein cholesterol (LDL) is the primary atherogenic agent. Although previously believed merely to collect passively within vessel walls, LDL is now felt to be a potent proinflammatory agent and creates the chronic inflammatory response characteristic of atherosclerosis (Maron, 2004). Logically, elevated levels of total and LDL cholesterol are associated with increased rates of coronary artery disease, ischemic stroke, and other atherosclerotic vascular complications (Horenstein, 2002; Law, 1994).

Preventively, the National Cholesterol Education Program Adult Treatment Panel-III (ATP-III) (2001) recommends that all adults 20 years and older have a serum lipoprotein profile drawn after a 9- to 12-hour fast once every 5 years. This profile includes total, LDL, and high-density lipoproteins and triglycerides. Table 1-16 lists interpretation of these levels. However, if other co-morbid risks for coronary heart disease are present, then LDL goals are more stringent.

Table 1-16 Interpretation of Cholesterol and Triglyceride Levels

Lipoprotein Type (mg/dL)	**Interpretation**
Total cholesterol	
<200	Optimal
200â€“239	Borderline elevated
≥240	Elevated
LDL cholesterol	
<100	Optimal
100â€“129	Near optimal
130â€“159	Borderline elevated
160â€“189	Elevated
≥190	Very elevated
HDL cholesterol	

<40	Low
≥60	Elevated
Triglycerides	
<150	Optimal
150â€“199	Borderline elevated
200â€“499	Elevated
≥500	Very elevated

HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Compiled from National Cholesterol Education Program, 2001, with permission.

Treatment

Lowering LDL cholesterol levels has been associated with reduced rates of myocardial infarction and stroke (Goldstein, 2006; Sever, 2003; Thavendiranathan, 2006). As seen in Table 1-17 and Fig. 1-9, therapy may include lifestyle changes with or without the addition of medication.

Table 1-17 Oral Lipid Lowering Agents

Drug Class and Agents	Brand Name	Major Indications	Starting Dose	Maximal Dose	Contraindications
HMG CoA reductase inhibitors 'statins'		Elevated LDL			Absolute: ▪ Active or chronic liver disease ▪ Pregnancy, lactation
Lovastatin	Mevacor, Altocor		20 mg qd	80 mg qd	
Pravastatin	Pravachol		40 mg qhs	80 mg qhs	
Simvastatin	Zocor		20 mg qhs	80 mg qhs	
Fluvastatin	Lescol		20 mg qhs	80 mg qhs	
Atorvastatin	Lipitor		10 mg qhs	80 mg qhs	
Rosuvastatin	Crestor		10 mg qhs	40 mg qhs	
Bile acid sequestrants		Elevated LDL			Absolute: ▪ Dysbetalipoproteinemia ▪ TG <400 mg/dL
Cholestyramine	Questran		4 g qd	24 g qd	
Colestipol	Colestid		2 g qd	16 g qd	
Colesevelam	Welchol		3750 mg qd	4375 mg qd	
Nicotinic acid		Elevated LDL, low HDL, elevated TG			Absolute: ▪ Chronic liver disease ▪ Peptic ulcer disease ▪ Severe gout
Immediate-release			100 mg tid	2 g tid	
Sustained-release			250 mg bid	1.5 g bid	
Extended-release	Niaspan		500 mg qhs	2 g qhs	
Fibric acids derivatives		Elevated TG, elevated			Absolute:

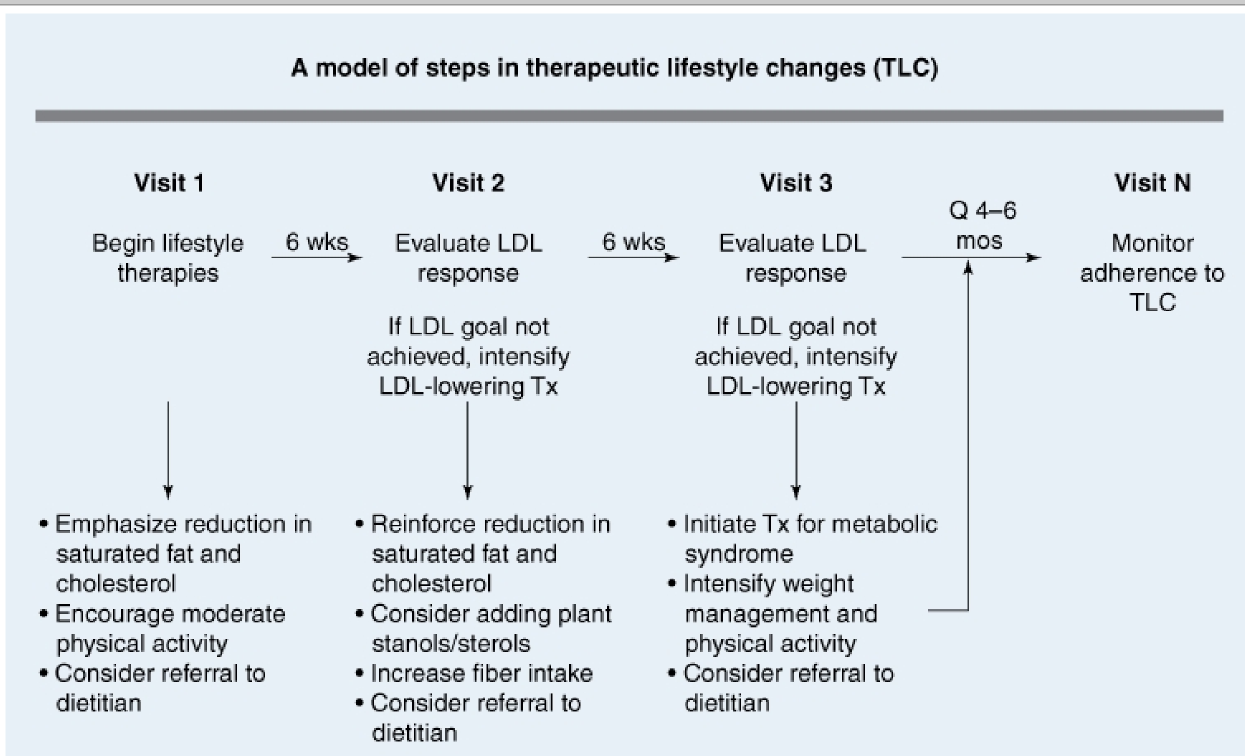
		remnants			■ Severe renal or liver disease ■ Gallbladder disease ■ Pregnancy, lactation
Gemfibrozil	Lopid, Gemcor		600 mg bid	600 mg bid	
Fenofibrate	Tricor		145 mg qd	145 mg qd	
Cholesterol absorption inhibitors		Elevated LDL			Relative: ■ Moderate or severe liver disease
Ezetimibe	Zetia		10 mg qd	10 mg qd	
Combination agent		Elevated LDL			Absolute: ■ Liver disease ■ Pregnancy, lactation
Ezetimibe/simvastatin	Vytorin		10 mg/10 mg qd	10 mg/80 mg qd	

bid = twice daily; CHD = coronary heart disease; GI = gastrointestinal; HDL = high-density lipoprotein cholesterol; HMG CoA = 3-hydroxy-3methylglutaryl coenzyme A; LDL = low-density lipoprotein cholesterol; TG = triglycerides; qd = daily; qhs = at bedtime; tid = three times daily; WHO = World Health Organization.

Cyclosporine, macrolide antibiotics, various antifungal agents, and cytochrome Pâ€“450 inhibitors should be used with appropriate caution with fibrates and niacin.

Compiled from National Cholesterol Education Program, 2001, and Rader, 2005, with permission.

FIGURE 1-9



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Algorithm for the use of lifestyle changes and medications in the management of hypercholesterolemia. Tx = treatment. *(Compiled from National Cholesterol Education Program, 2001.)*

For those with depressed HDL levels, efforts should be directed toward reaching LDL goals. Additionally, weight management and increased physical activity should be included.

HYPERTRIGLYCERIDEMIA

Triglycerides are delivered to tissues by very-low-density lipoprotein (VLDL), which is synthesized and secreted by the liver. This triglyceride-rich lipoprotein is taken up by adipose tissue and muscle, where triglycerides are cleaved from VLDL. Ultimately, a VLDL remnant is created that is atherogenic. For this reason, triglyceride levels can be used as one marker for atherogenic lipoproteins, and high triglyceride levels have been linked to increases in cardiovascular disease (Assmann, 1996; Austin, 1998). Additionally, its clinical importance is underscored by its inclusion as a criterion for the metabolic syndrome (see Table 1-15) (Dunbar, 2005).

Hypertriglyceridemia is diagnosed based on criteria found in Table 1-16. For most with mild or moderate triglyceride elevation, recommendations from ATP-III attempt to lower both LDL and VLDL levels. Alternatively, for those with triglyceride levels greater than 500 mg/dL, treatment goals focus primarily on triglyceride levelâ€"lowering to prevent pancreatitis.

Stroke

Stroke is the third leading cause of death in the United States, and each year approximately 373,000 American women suffer a new or recurrent stroke. Primary prevention is important, as greater than 70 percent of strokes are first events (American Heart Association, 2005). Primary care providers should be aware of modifiable risk factors for stroke and treat or refer women for treatment of these factors (Table 1-18).

Table 1-18 Risk Factors and Treatment Results for Stroke

Risk Factor	Relative Risk	Relative Risk Reduction with Treatment
Hypertension	2â€"5	38%
Atrial fibrillation	1.8â€"2.9	68% with warfarin, 21% with aspirin
Diabetes	1.8â€"6	No proven effect
Smoking	1.8	50% at 1 year, baseline risk at 5 years postcessation
Hyperlipidemia	1.8â€"2.6	10â€"29%
Carotid stenosis	2.0	29â€"65%

From Smith, 2007, with permission.

Exercise

Exercise has known benefits in preventing coronary artery disease, type 2 diabetes, osteoporosis, obesity, depression, insomnia, and breast and colon cancers (Brosse, 2002; Knowler, 2002; Lee, 2003; Vuori, 2001; Youngstedt, 2005). Many of these associations may result from the effects of exercise to lower blood pressure, decrease LDL cholesterol and triglyceride levels, increase HDL cholesterol levels, improve blood sugar control, and reduce weight (Braith, 2006; Pescatello, 2004; Sigal, 2004).

Despite these benefits, based on 2004 U.S. statistics, 66 percent of all women do not participate in leisure-time physical activity lasting longer than 10 minutes, and only 9 percent exercised more than 5 times per week (Lethbridge-Cejku, 2006). Recommendations from the Centers for Disease Control and Prevention (2006) include moderate-intensity activity such as walking, water aerobics, or yardwork for at least 30 minutes on 5 or more days each week *or* vigorous-intensity activities such as running, swimming laps, or circuit weight training for 20 to 60 minutes per session on at least 3 days each week. A fuller listing of general physical activities and their intensity descriptions can be found at the CDC website:

http://www.cdc.gov/nccdphp/dnpa/physical/pdf/PA_Intensity_table_2_1.pdf .

Although exercise programs have traditionally emphasized dynamic, aerobic lower-extremity exercise, research increasingly suggests that complementary resistance training improves muscular strength and endurance, cardiovascular function, metabolism rate, coronary risk factors, and psychosocial well-being (Pollock, 2000). Table 1-19 compares the different advantages offered by aerobic and resistance training.

Table 1-19 Effects of Aerobic and Resistance Training

Variable	Aerobic Exercise	Resistance Exercise
Bone mineral density	↑	↑↑↑
Body composition		
Fat mass	↓↓	↓
Muscle mass	↔	↑↑
Strength	↔	↑↑↑
Glucose metabolism		
Insulin response to glucose challenge	↓↓	↓↓
Basal insulin levels	↓↓	↓
Insulin sensitivity	↑↑	↑↑
Serum lipids		
High-density lipoprotein	↑↔	↑↔
Low-density lipoprotein	↓↔	↓↔
Resting heart rate	↓↓	↔
Blood pressure at rest		
Systolic	↓↓	↓
Diastolic	↓↓	↓
Physical endurance	↑↑↑	↑↑
Basal metabolism	↑	↓↓

↑ = indicates increased; ↓ = decreased; ↔ = negligible effect

From Braith, 2006, with permission.

Thyroid Disease

Dysfunction of the thyroid gland may lead to increased or decreased gland activity. As a result, symptoms of thyroid disease may vary widely, but commonly include changes in weight, temperature tolerance, menstruation, energy level, mood, skin and hair, and gastrointestinal motility. The risk of thyroid disease increases with age, and dysfunction is significantly more common in women.

Accordingly, the American Thyroid Association recommends that adults, especially women, be screened for thyroid dysfunction by measurement of a serum thyroid-stimulating hormone (TSH) concentration, beginning at age 35 years and every 5 years thereafter (Ladenson, 2000). Moreover, individuals with clinical manifestations potentially attributable to thyroid dysfunction and those with risk factors for its development may require more frequent testing. People at higher risk for thyroid dysfunction include the elderly, postpartum women, those with prior exposure to high levels of radiation (>20 mGy), and those with Down syndrome. In contrast, the U.S. Preventive Services Task Force (2004) has found insufficient evidence to recommend for or against routine screening.

Mental Health

DEPRESSION, DOMESTIC VIOLENCE, AND SUBSTANCE ABUSE

These problems are pervasive and account for significant morbidity and mortality. Each is discussed in detail in Chapter 13, Common Psychiatric Presentations, and should be routinely screened for at annual visits. For depression, few data support the use of one specific screening method, and simple questions such as "During the past 2 weeks, have you felt down, depressed, or hopeless?" and "Have you felt little interest or pleasure in doing things?" are often effective (Whooley, 1997). All positive screening tests should prompt evaluation for depression as outlined in Chapter 13 (see Table 13-5).

The American College of Obstetricians and Gynecologists (2002) guidelines on domestic violence recommend that physicians routinely ask women direct, specific questions about abuse. General introductory statements such as "Because abuse and violence are so common in women's lives, I've begun to ask about it routinely" and providing The National Domestic Safety Hotline number 1-800-799-SAFE (7233) may be used (American Medical Association, 1992).

Smoking

Cigarette smoking is the single most preventable cause of death in the United States and has been linked with certain cancers, cardiovascular disease, chronic lung diseases, and stroke (National Cancer Institute, 2004). Yet despite these known effects, in 2003, only 64 percent of U.S. smokers who had routine examinations were advised by a physician to quit smoking (Torrijos, 2006). Strategies for cessation may include counseling and pharmacotherapy, and both yield increased abstinence rates (Ranney, 2006).

Smoking Pharmacotherapy

Nicotine is the key addictive component of tobacco, and it binds to the nicotinic acetylcholine (Ach) receptor (Coe, 2005; Tapper, 2004). Binding increases central nervous system (CNS) dopamine levels. With smoking cessation, CNS dopamine levels are immediately lowered and cravings follow.

To blunt withdrawal symptoms, several products have been developed. These pharmacologic agents can broadly be divided into (1) nicotine replacement agents, (2) CNS agents, and (3) nicotine agonists (Table 1-20). Of these, nicotine replacement agents lower nicotine levels gradually, thereby blunting nicotine withdrawal symptoms, and increasing the probability of smoking cessation. Of the CNS agents, bupropion is a dopamine reuptake inhibitor. This drug may maintain central levels of dopamine during cessation and diminish dopamine withdrawal symptoms. Finally, varenicline is a nicotinic Ach-receptor partial agonist. In theory, varenicline (Chantix, Pfizer, New York, NY) binds to the nicotinic Ach receptor to relieve withdrawal symptoms. All of these are effective. Wu and colleagues (2006), however, in their meta-analysis of controlled trials found higher rates of cessation after 1-year following varenicline.

Table 1-20 Drugs Used for Smoking Cessation					
Agent	**Brand Name**	**Initial Dosing**	**Maintenance**	**Drug Tapering**	**Therapy Duration**
Nicotine replacement					
Patch	Habitrol Nicoderm CQ	For those smoking >10 cigs/d: a 21-mg patch is reapplied daily	After 2 wks, 14-mg patch is used	For the final 2 wks, a 7-mg patch is used for both groups	8-12 wks
		For those smoking <10 cigs/d: 14-mg patch	After 2 wks, 14-mg patch cont'd		
Gum	Nicorette	1 piece every 1-2 hr	1 piece every 2-4 hr	1 piece every 4-8 hr	12 wks
Inhaler	Nicotrol		6 (average use) to 16 cartridges puffed qd for 12 wks	Cartridge use is then tapered	12-24 wks
Nasal spray	Nicotrol		1 spray to each nostril per hr		12 wks
Nicotine agonists					
Varenicline	Chantix	0.5 mg PO qd for 1-3 d, then 0.5 mg PO bid for next 1-3 d	1 mg PO bid		12 wks
CNS agents					
Buproprion	Wellbutrin SR Zyban	150 mg PO qd for 3 d; begun 1-2 wks prior to cessation	150 mg PO bid		12 wks
Nortriptyline[a]		25 mg PO qd begun 2-4 wks prior to cessation	75-100 mg PO qd		12 wks
Clonidine[a]	Catapres	0.1 mg PO qd or bid, increase by 0.10 mg/d each wk as needed	0.15-0.75 mg PO qd		3-10 wks
	Catapres-TTS	0.1-mg transdermal patch is changed weekly	0.1- to 0.2-mg transdermal patch weekly		

bid = twice daily; CNS = central nervous system; PO = orally; qd = daily.

[a] Recommended as second-line agents by U.S. Public Health Service clinical guidelines, 2000.

From the U.S. Department of Health and Human Services Public Health Service, 2000, with permission.

Alcohol Abuse

Simple direct questions regarding use can be brief yet effective tools to identify potential alcohol abuse (Fleming, 2005). If usage patterns suggest abuse, then further evaluation or referral is warranted. The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV-TR) criteria for substance dependence or substance abuse are found in Tables 13-9 and 13-10.

INSOMNIA

Insomnia is common and its definition includes: (1) difficulty initiating sleep, (2) trouble maintaining sleep, and (3) early waking. Insomnia may be primary or may be secondary to other conditions such as depression, cross-time-zone travel, restless leg syndrome, stimulant use, and sleep apnea (National Institutes of Health, 2005). Accordingly, a historical inventory should be taken to investigate such complaints and treatment should be directed to these and other secondary causes (Becker, 2005).

Treatment of primary insomnia is typically cognitive-behavioral or pharmacologic. Behavioral therapies are varied and include those that control sleep timing and duration, attempt to improve the bedroom environment, or focus on relaxation techniques (Silber, 2005). Medications may be used to aid sleep, and most agents are of the benzodiazepine family (Table 1-21).

Table 1-21 Medications for Insomnia Approved by the U.S. Food and Drug Administration

Medication	Duration of Action	Dose	Indications
Benzodiazepines			
Temazepam (Restoril)	Intermediate	7.5â€“30 mg	For sleep-maintenance insomnia
Estazolam (ProSom)	Intermediate	0.5â€“2 mg	For sleep-maintenance insomnia
Triazolam (Halcion)	Short	0.125â€“0.25 mg	For sleep-onset insomnia
Benzodiazepine-receptor agonists			
Eszopiclone (Lunesta)	Intermediate	1â€“3 mg	For sleep-maintenance insomnia
Zolpidem (Ambien)	Short	5â€“10 mg	For sleep-onset insomnia
Zaleplon (Sonata)	Ultrashort	5â€“20 mg	For sleep-onset or sleep-maintenance insomnia
Melatonin-receptor agonist			
Ramelteon (Rozerem)	Short	8 mg	For sleep-onset insomnia

Abbreviated from Silber, 2005, with permission.

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TECHNIQUES USED FOR IMAGING IN GYNECOLOGY: INTRODUCTION

Over the past several decades, there have been a number of technical advances that currently allow for superb imaging of female pelvic structures. The evolution of sonography has led to use almost equivalent to that in obstetrics. Radiography and contrast hysterosalpingography (HSG) have all but been replaced by computed-tomographic (CT) scanning with its excellent pelvic organ resolution. In addition, magnetic resonance (MR) imaging is now readily available in most centers and has literally added new dimensions to pelvic imaging.

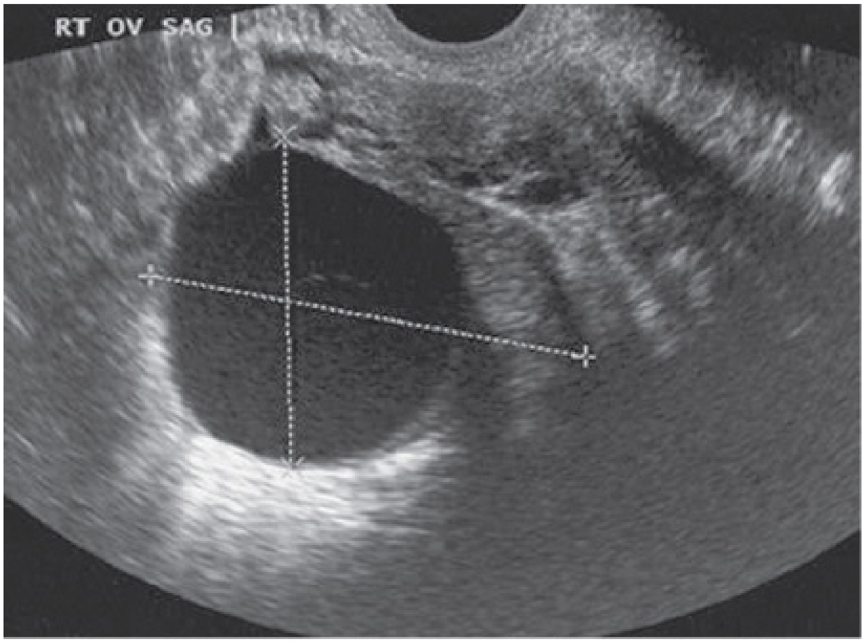
SONOGRAPHY

Physics

In sonography, the image displayed on a screen is produced by sound waves reflected back from an imaged structure. Alternating current is applied to a transducer containing piezoelectric crystals, which convert electric energy to high-frequency sound waves. A water-soluble gel applied to the skin acts as a coupling agent. Sound waves pass through layers of tissue, encounter an interface between tissues of different densities, and are reflected back to the transducer. Converted back into electric energy, they are displayed on a screen. Dense material such as bone, or a synthetic material such as an intrauterine device, produces high-velocity reflected waves, also termed *echoes* , which are displayed on a screen as white. Materials such as these are described as *echogenic* . Conversely, fluid is anechoic, generates few reflected waves, and appears black on a screen. Images are generated so quicklyâ€”more than 40 frames/secondâ€"that the picture on the screen appears to move in real-time (Cunningham, 2005b).

Reflection of sound is greatest when there is a large difference between the acoustic impedance of two structures, which explains why cysts are so well demonstrated with sonography. Strong echoes are produced from the cyst walls but no echoes arise from fluid within the cyst. As more sound traverses the cyst, more echoes are received from the area behind the cyst, a feature known as *through-transmission* or *acoustic enhancement* (Fig. 2-1). Conversely, with a calcified structure, there is a reduction in sound passing through, which causes a band of reduced echoes beyond it, known as *acoustic shadowing* (Fig. 2-2) (Armstrong, 2001).

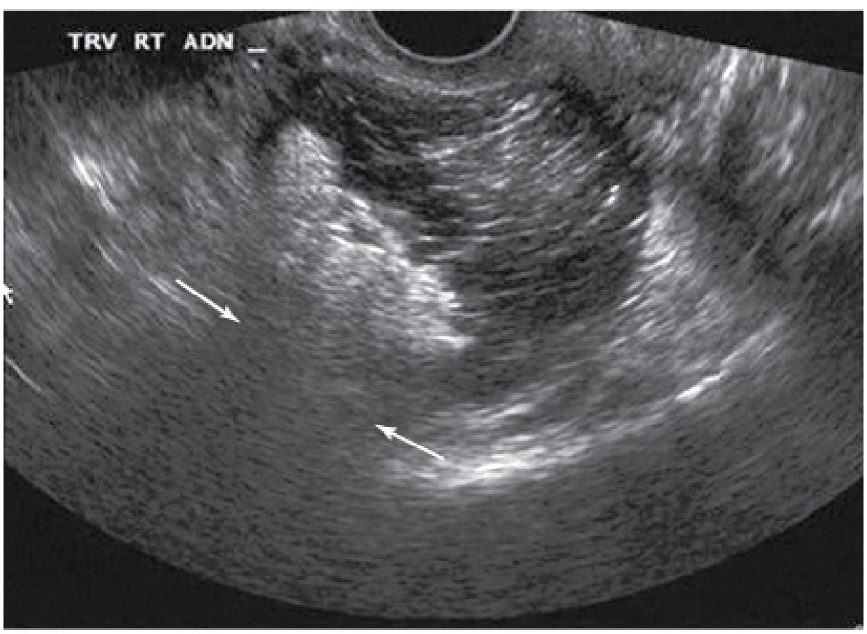
FIGURE 2-1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Transvaginal sonogram of a premenopausal ovary containing a follicular cyst. The cyst fluid appears black or anechoic. Note the white or hyperechoic area under the cyst, a sonographic feature called posterior acoustic enhancement or through-transmission. *(Courtesy of Dr. Elysia Moschos.)*

FIGURE 2-2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Transvaginal sonogram of an ovarian teratoma demonstrating posterior acoustic shadowing (**arrows**). *(Courtesy of Dr. Elysia Moschos.)*

Examination Techniques

Guidelines for sonographic examination of the female pelvis have been established by the American Institute of Ultrasound in Medicine (2005). These were developed to serve as standards of quality assurance for patient care and to provide assistance to practitioners performing sonography. Guidelines describing equipment and documentation may be accessed at http://www.aium.org/publications/clinical/pelvis.pdf .

All probes should be cleaned after each examination, and vaginal probes should be covered by a protective condom sheath prior to insertion. A female staff member should always chaperone patients undergoing transvaginal sonography (TVS). Guidelines describe the examination to be performed for each organ and anatomic region in the female pelvis. For instance, in evaluating the uterus, the following should be documented: uterine size, shape, and orientation; and a description of the endometrium, myometrium, and cervix. A permanent record of the examination and its interpretation should be appropriately labeled and placed in the medical record. A copy is also kept by the facility performing the study.

TRANSABDOMINAL SONOGRAPHY

A variety of examination techniques can be used for the sonographic study of the female pelvis. In a nonpregnant woman, transabdominal evaluation, using a curved-array 3- to 5-mHz transducer, is still considered the first approach because it provides global identification of all pelvic organs and their special relationships to one another (American Institute of Ultrasound in Medicine, 2005). A full bladder is usually necessary for adequate visualization, as it pushes the uterus upwards from behind the pubic symphysis and displaces small bowel from the field of view. Moreover, the bladder acts as an acoustic window to improve transmission of sound waves. In patients with large lesions or masses located superior to the bladder dome, only the panoramic capabilities provided by transabdominal sonography allow complete evaluation of the disease process (Fleischer, 1997a). Still, evaluation of the endometrial cavity may be problematic with a transabdominal approach, often necessitating the use of the transvaginal technique.

TRANSVAGINAL SONOGRAPHY

This modality uses higher-frequency (5- to 10-mHz) transducers, which increase sensitivity and spatial image resolution. The probe is positioned in the vaginal fornices, thus the transducer is closer to the region of interest, and there is less beam attenuation in superficial soft tissues. In contrast to transabdominal imaging, the bladder is emptied prior to performing a transvaginal study.

TRANSRECTAL AND TRANSPERINEAL TECHNIQUES

Transrectal probes or conventional transducers placed over the perineal region are much less commonly employed. They are used for selected indications such as those discussed further in the section on pelvic floor imaging (Pelvic Floor).

HARMONIC IMAGING

This recent modification of sonography is designed to improve tissue visualization by reducing artifacts, particularly those that arise from superficial structures such as adipose tissue, by using harmonics of the transmitted ultrasound beam (Armstrong, 2001).

FOCUSED ULTRASOUND THERAPY

Ultrasound energy during conventional imaging propagates harmlessly through tissue with small amounts of energy being absorbed. This energy is deposited as heat but is dissipated by the cooling effects of perfusion and conduction. No harmful effects have been recorded at the intensities used for diagnostic purposes (American Institute of Ultrasound in Medicine, 1991).

If, however, the ultrasound beam carries a high level of energy and is brought to a tight focus, energy carried by the beam is rapidly converted into heat with an increase in temperature (ter Haar, 1999). When target spot temperatures rise higher than 55Â°C, proteins are denatured, cell death occurs, and coagulative necrosis is created (Lele, 1977). In contrast, surrounding tissues are warmed, but not to lethal temperatures. This technique may be used in the treatment of leiomyomas and discussed later in the chapter.

DOPPLER TECHNOLOGY

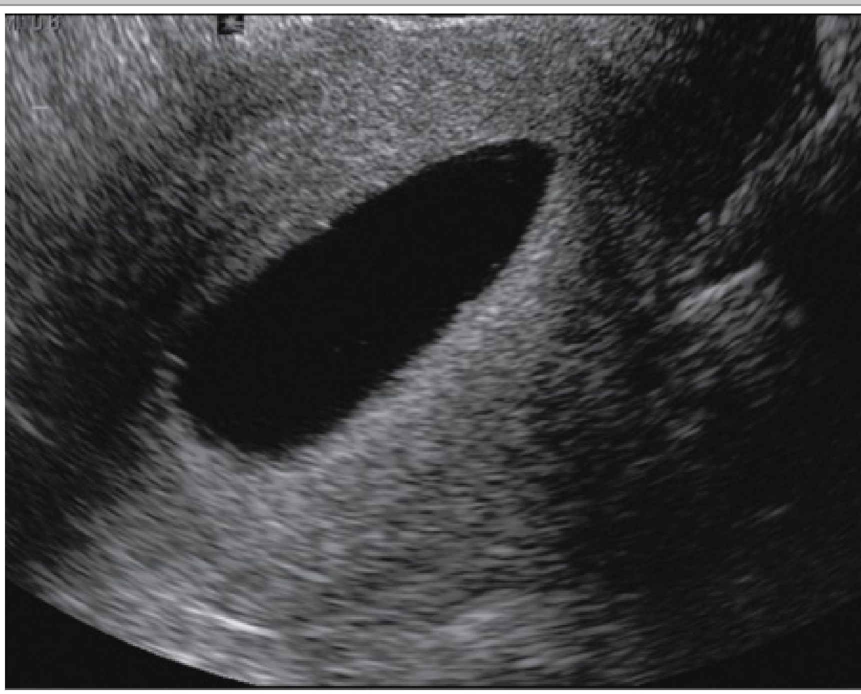
This modality can be performed with either transabdominal or transvaginal sonography to determine blood flow through pelvic organs. Of Doppler parameters, the resistive index and pulsatility index are commonly calculated. These describe the impedance to blood flow within and to the organ of interest.

Applications of color Doppler in gynecology include evaluation of ovarian masses for torsion or malignancy, improved detection of extrauterine vascularity associated with ectopic pregnancy, and assessment of uterine perfusion in patients with leiomyomas and endometrial disorders.

Saline-Infusion Sonography

Also called sonohysterography, saline-infusion sonography (SIS) was developed to obtain a more detailed view of the endometrial cavity (Hill, 1997). After voiding, a woman undergoes a comprehensive transvaginal sonographic evaluation. A vaginal speculum is then inserted, the vagina and cervix are swabbed with an antiseptic solution, and a catheter primed with sterile saline is advanced into the cervical canal and past the internal os. We do not routinely use a tenaculum for this. Touching the uterine fundus when advancing the catheter should be avoided, as this can induce pain or vasovagal response. It may also shear away endometrium, causing false-positive results. The speculum is carefully removed to avoid dislodging the catheter, the transvaginal probe is reinserted, and sterile saline is injected through the catheter at a rate based on the patient's tolerance. Usually not more than 10 to 20 mL is required to distend the endometrial lumen (Fig. 2-3). During this time, the cavity is observed with transvaginal sonography. The sonographer scans in the longitudinal plane, imaging from one cornu to the other, and in the transverse plane from the fundus to the cervix. Any irregularities of the endometrial surface are well-delineated by the hypoechoic contrast of the saline. At the procedure's conclusion, the catheter is withdrawn under sonographic visualization so that the uterine isthmus and endocervical canal may be evaluated. On average, the procedure lasts 5 to 10 minutes.

FIGURE 2-3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Saline-infusion sonography of a normal endometrial cavity. *(Courtesy of Dr. Elysia Moschos.)*

There are many different catheter systems, including rigid systems and flexible catheters with and without attached balloons. We

use a 7F hysterosalpingography (HSG) balloon catheter set (Cooper Surgical, Trumball, CT) and have found it easy to place and well tolerated (Fig. 2-4). Several distending solutions have been described, including saline, lactated Ringer solution, and 1.5-percent glycine. We have found that sterile saline is inexpensive and provides excellent imaging.

FIGURE 2-4

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Saline-infusion sonography catheter. *(Courtesy of Dave Gresham.)*

In the premenopausal woman, SIS is best performed within the first 10 days of the menstrual cycle, and optimally on cycle days 4, 5, or 6, when the endometrial lining is thinnest. This timing is recommended to avoid misinterpretation of menstrual blood clots as intrauterine pathology or conversely, to miss pathology obscured by thick endometrial growth (Hill, 1997). In addition, such timing should usually preclude pregnancy. For the postmenopausal woman, timing of the procedure is not cycle-dependent.

Complications of SIS are minimal, and the risk of infection is less than 1 percent (Bonnamy, 2002). Most recommend prophylactic antibiotics for women with a history of pelvic inflammatory disease and in those who require bacterial endocarditis prophylaxis. We also routinely give a single dose of doxycycline, 200 mg orally, following SIS in women with diabetes. Although not evidence-based, we also choose to provide prophylaxis to infertile patients because of the risk for significant tubal damage associated with pelvic infection. Pain is usually minimal. During SIS, it has been our experience that women who have undergone tubal ligation have more discomfort, likely because fluid cannot efflux through the tubes. A nonsteroidal anti-inflammatory drug given 30 minutes prior to the procedure will typically minimize any potential discomfort.

Contraindications to SIS include hematometra, pregnancy, active pelvic infection, or obstruction such as with an atrophic or stenotic cervix or vagina. In postmenopausal women with cervical stenosis, we have found use of a paracervical block, a tenaculum for traction on the cervix, and a sonographically-guided sequential cervical dilation with lacrimal duct dilators to be helpful.

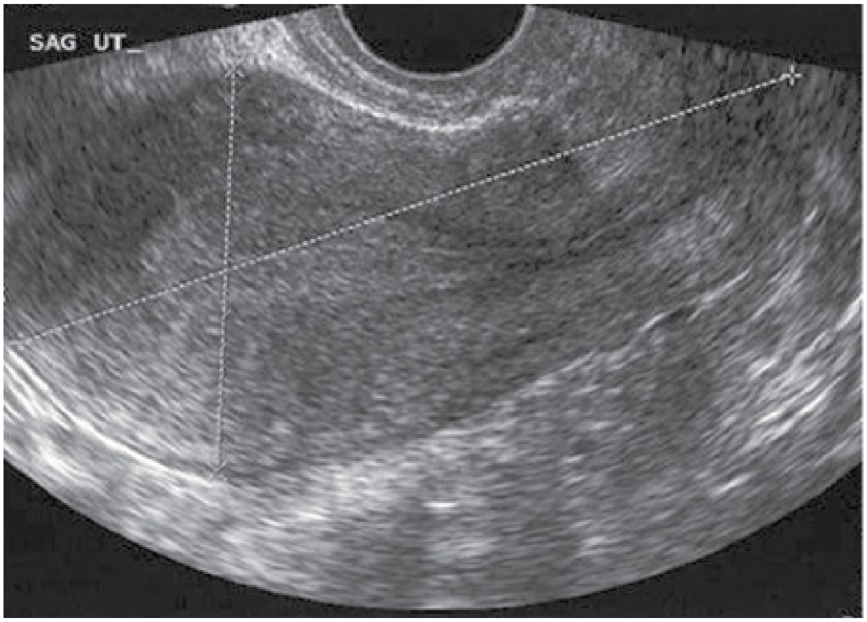
Normal Anatomy with Sonography

REPRODUCTIVE TRACT ORGANS

In the reproductive years, a normal uterus measures approximately 7.5 × 5.0 × 2.5 cm, but is smaller in the prepubertal, postmenopausal, or hypoestrogenized woman. Normal uterine stroma returns low-level, uniform echoes, and the position of the endometrial and endocervical canals is indicated by linear echogenic stripes, representing the interfaces between mucus and mucosa (Fig. 2-5). The cervix is best visualized transvaginally with the tip of the probe about 2 to 3 cm from it. The endocervical

canal is a continuation of the endometrial cavity and appears as a thin echogenic stripe (Fig. 2-6). The vagina is seen as a hypoechoic tubular structure with an echogenic lumen that curves inferiorly over the muscular perineal body at the introitus. The ovaries are ellipsoid, and normally lie in the ovarian fossa with their long axes parallel to the internal iliac vessels and the ureters, which lie posteriorly (Fig. 2-7). Ovarian volume ranges from 4 to 10 cm^2 depending on hormonal status (Cohen, 1990). Ovarian follicles appear as spherical anechoic structures within the ovary and may reach a normal size of 2.5 cm. Normal fallopian tubes are not visible. A small amount of fluid in the posterior cul-de-sac is a normal finding and is often seen with ovulation.

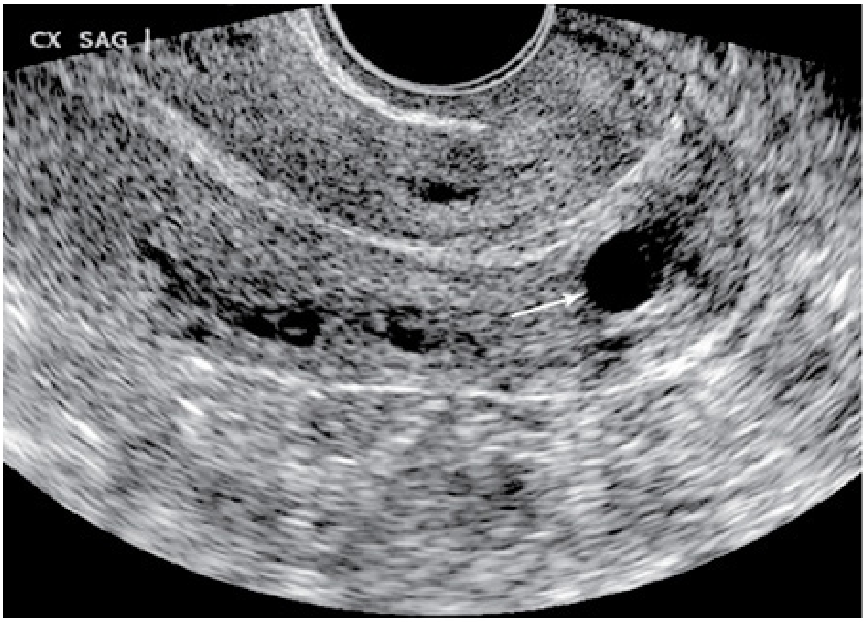
FIGURE 2-5



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Transvaginal sonogram in the sagittal plane of an anteverted, anteflexed uterine corpus. Calipers demonstrate measurements of the uterine length (+) and the anterior-posterior dimension (x). *(Courtesy of Dr. Elysia Moschos.)*

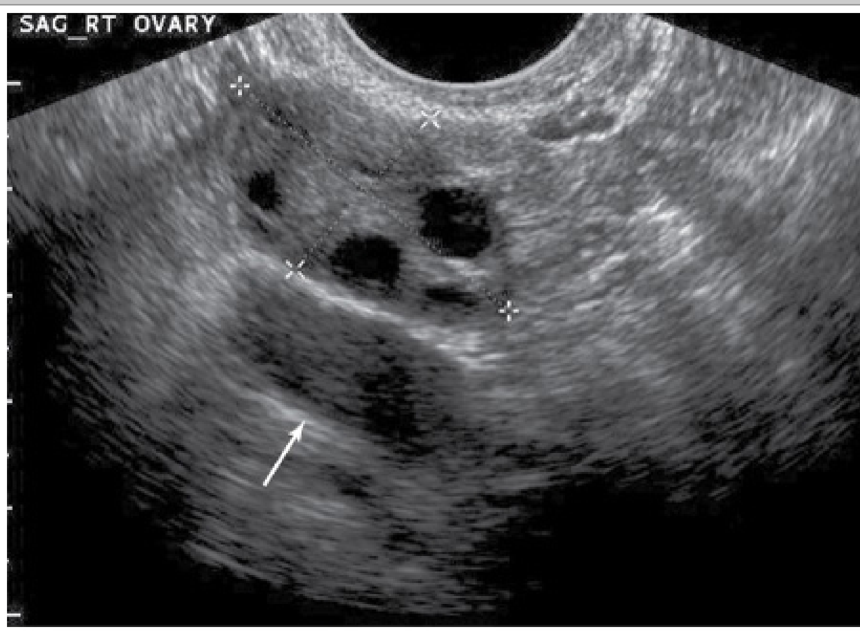
FIGURE 2-6



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Transvaginal sonogram in the sagittal plane of the uterine cervix. Arrow points to an endocervical cyst seen posterior to the thin, echogenic endocervical canal. *(Courtesy of Dr. Elysia Moschos.)*

FIGURE 2-7



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

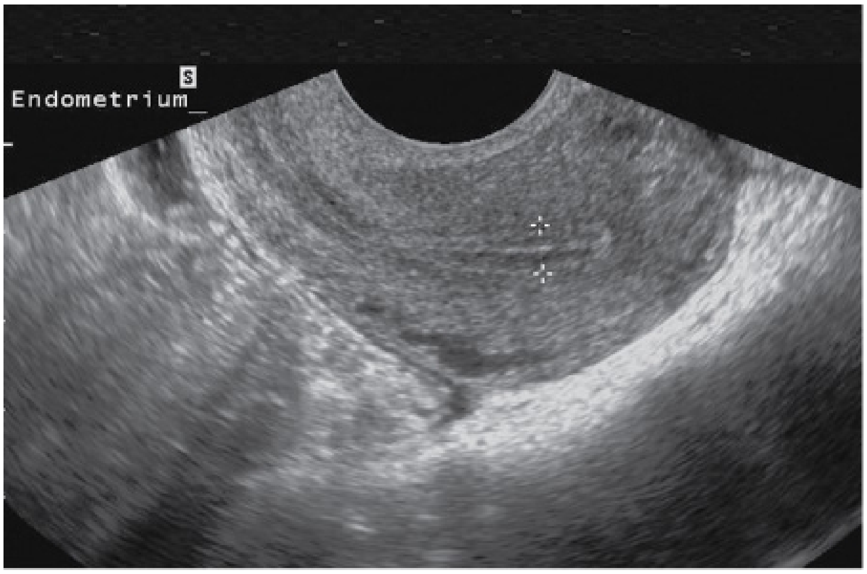
Transvaginal sonogram in the sagittal plane of a left ovary in a premenopausal woman. The ovary normally lies in the ovarian fossa, anterior to the internal iliac vessels, as identified by the **arrow** . *(Courtesy of Dr. Elysia Moschos.)*

ENDOMETRIUM

Functionally, the endometrium has two main layers: the stratum basale, which comprises the densely cellular supporting stroma and varies little with the phase of the cycle, and the stratum functionale, which proliferates during each cycle and partially desquamates at menses (see Fig. 8-2). These layers cover the entire cavity.

Sonographic appearances of the endometrium during the menstrual cycle correlate with the phasic changes in its histologic anatomy. During the follicular phase, when the endometrium is under the influence of estrogen from ovarian folliculogenesis, the stratum basale appears echogenic due to spectral reflections from the mucus-laden glands. In contrast, the stratum functionale is relatively hypoechoic because of the orderly arrangement of glands that lack secretions. The central opposing surfaces of these two endometrial layers manifest as a highly reflective, thin midline strip, and the three echogenic lines give a characteristic tri-laminar appearance of the proliferative endometriumâ€"the endometrial stripe (Figs. 2-8 and 8-6).

FIGURE 2-8



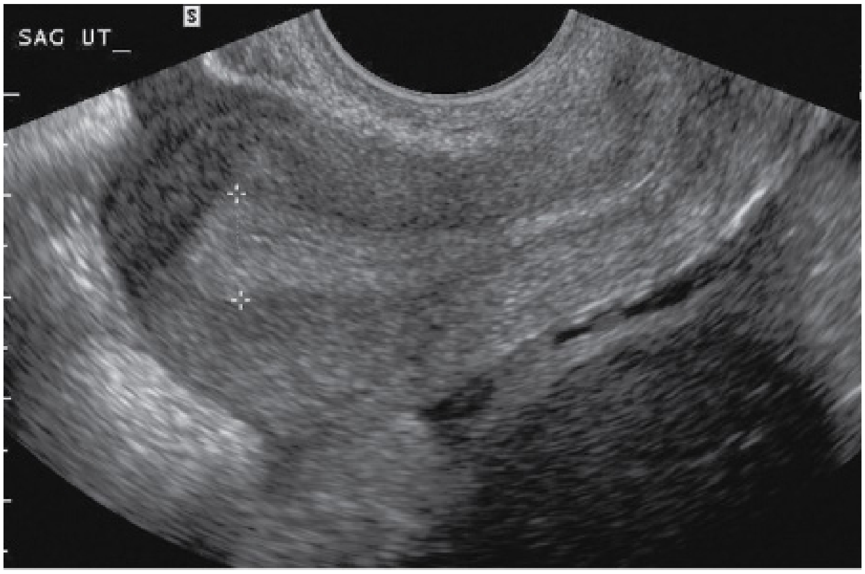
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Transvaginal sonogram in the sagittal plane of the characteristic tri-laminar proliferative endometrium. Calipers demonstrate proper measurement of the "double-layer" thickness made of the alternating hyper-hypo-hyperechogenic lines. *(Courtesy of Dr. Elysia Moschos.)*

Endometrial thickness is measured from the echogenic interface of the anterior basale layer to the echogenic interface of the posterior basale layer, thus representing a "double thickness". The hypoechoic halo outside of and adjacent to the endometrium should not be included in the measurement, as this is actually the inner compact layer of myometrium. Sonographically, the endometrium should be measured from a sagittal or long-axis image of the uterus in the plane in which the endometrial stripe is seen contiguous with the endocervical canal and distinct from the myometrium. Endometrial thickness correlates approximately with the day of the cycle up to day 7 or 8 (Richenberg, 2000).

With ovulation and progesterone production from the corpus luteum during the secretory phase, glandular enlargement and appearance of secretory vacuoles begins. These changes are seen sonographically (Fig. 2-9). During this phase, the endometrium achieves its maximum thickness as the stroma becomes more vascular and edematous.

FIGURE 2-9

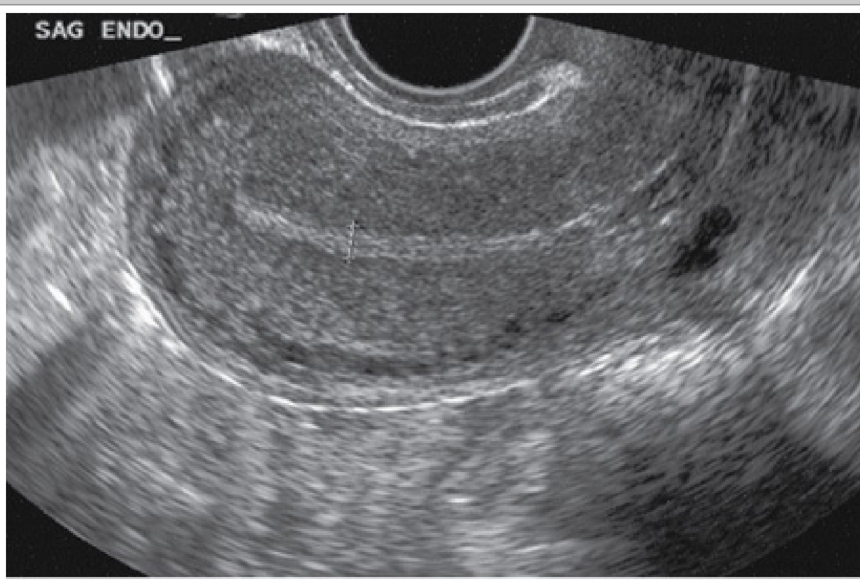


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Transvaginal sonogram in the sagittal plane of a secretory endometrium. The endometrium has become uniformly echogenic. *(Courtesy of Dr. Elysia Moschos.)*

With menstruation, the endometrium appears as a slightly irregular echogenic interface from sloughed tissue and blood. The thinnest measurements of endometrium are found at the conclusion of menses (Fig. 2-10).

FIGURE 2-10

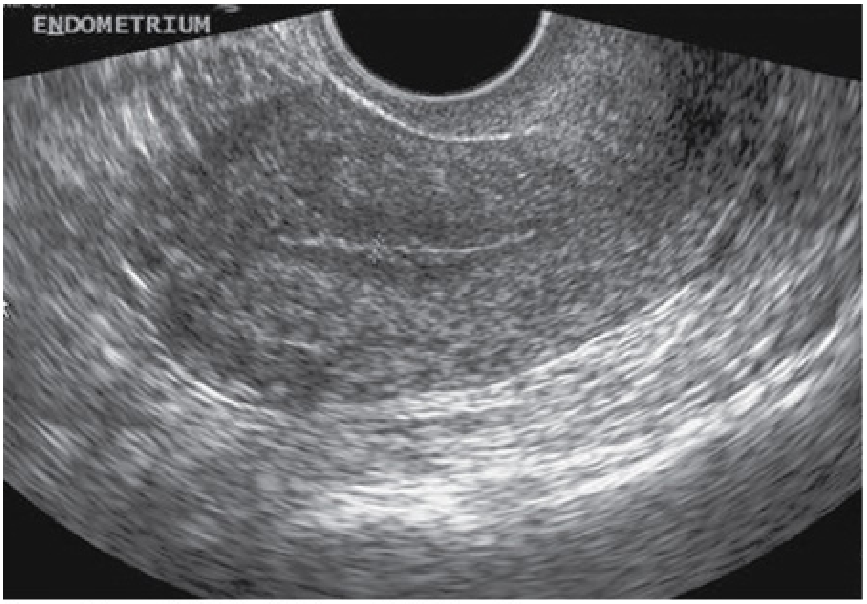


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Transvaginal sonogram in the sagittal plane of a menstrual-phase endometrium. *(Courtesy of Dr. Elysia Moschos.)*

With cessation of estrogen stimulation beginning at menopause, the endometrium atrophies, and there is no further cyclic sloughing. The postmenopausal endometrium appears thin and uniform (Fig. 2-11).

FIGURE 2-11



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Transvaginal sonogram in the sagittal plane of an atrophic postmenopausal endometrium. *(Courtesy of Dr. Elysia Moschos.)*

PELVIC FLOOR

With the advent of urogynecology as a specialty, sonography is widely used to evaluate pelvic floor anatomy and function. Various two-dimensional techniques, including transvaginal, transrectal, transperineal, and intraurethral sonography, have been used to investigate urethral anatomy.

Transrectal sonography was the first technique used to assess anal sphincter morphology after childbirth. This method requires special equipment as well as distension of the anal canal (see Chap. 25, Endoanal Ultrasonongraphy). The technique is of limited value during the immediate postpartum period, and it only provides information about anal sphincter morphology. Thus, without levator ani muscle assessment, it cannot be used to completely evaluate the posterior compartment (Wisser, 2001).

Alternatively, assessment of anorectal morphology and the pelvic floor have been described with vaginal sonography. This approach uses a rotating endorectal probe or standard transvaginal probe (Sandridge, 1995; Sultan, 1994).

Perineal sonography has been used more recently to evaluate the pelvic floor. The technique requires filling the bladder with approximately 300 mL of saline. With a woman either supine or erect, a 5-MHz curved-array transducer is placed in a sagittal orientation to the perineum. This allows real-time imaging of the symphysis, urethra, bladder neck, and bladder. Measurements have been standardized by Schaer and colleagues (1995).

Clinical Applications

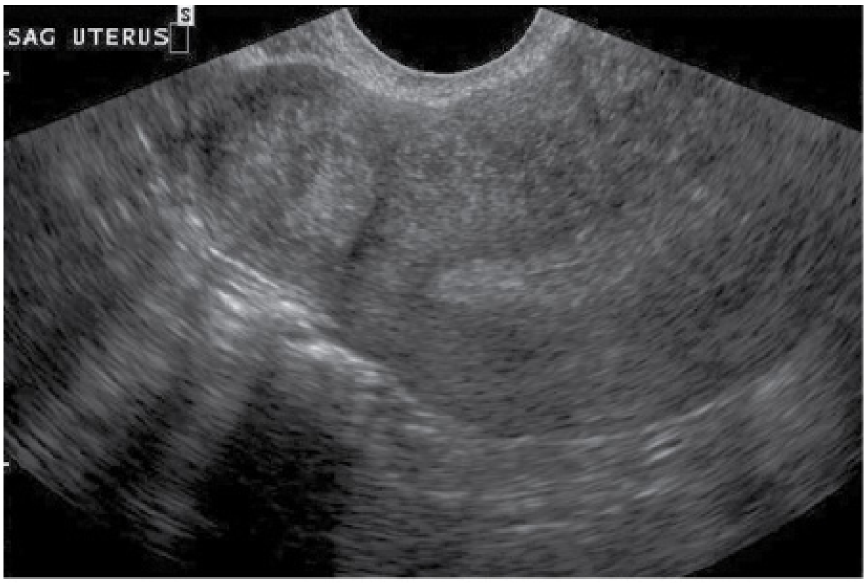
Transvaginal sonography (TVS) is preferred for evaluation of the normal uterus and adnexa and for diagnosis of gynecologic diseases. These include diagnosis and management of ectopic pregnancy, support for infertility practices, and early detection of ovarian and endometrial cancer.

Transvaginal sonography has few limitations. The only two absolute contraindications are imperforate hymen and patient refusal. A relative contraindication is the patient with a virginal or strictured introitus. These women, however, can usually undergo comfortable examination with proper counseling.

LEIOMYOMAS

When visualized with sonography, uterine leiomyomas usually appear as solid, discrete, well-defined masses with a thin hypoechoic periphery (Fig. 2-12). Although most often hypoechogenic in relation to the myometrium, they may also appear hyper- or isoechogenic (see Fig. 9-6) (Lyons, 2000). Shadowing at their lateral borders is common.

FIGURE 2-12



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Transvaginal sonogram of a fundal subserosal leiomyoma (**arrow**). *(Courtesy of Dr. Elysia Moschos.)*

Sonography is used by most as the imaging technique for preoperative assessment of women who undergo uterine artery embolization (UAE) for symptomatic leiomyomas. In these women, three-dimensional color Doppler sonography can accurately depict fibroid vascularity, and in some cases, collateral flow is seen that is not detected by uterine arteriography (Muniz, 2002). Doppler flow measurements are also useful to predict outcomes of leiomyoma embolization such as tumor shrinkage and treatment failure (McLucas, 2002). Sonography can also be used to document volume decreases of leiomyomas following gonadotropin-releasing hormone (GnRH) agonist therapy (Fleischer, 2000).

ADENOMYOSIS

Sonographic diagnosis of adenomyosis is difficult and based on findings that may be very subtle. When evaluated by Doppler sonography, adenomyosis lesions are vascularized and vessels appear less well-organized than those in the normal myometrium (Atri, 2000; Reinhold, 1999). Although MR imaging is still considered the gold standard for diagnosis of adenomyosis, careful analysis of these transvaginal sonographic findings has shown greater than 80-percent sensitivity and 70-percent specificity (Fedele, 1992; Reinhold, 1995).

ENDOMETRIAL ABNORMALITIES

Transvaginal sonography is used to accurately evaluate the thickness and appearance of the endometrium, and together with SIS, plays an important role in the management of endometrial disorders. It is commonly employed to aid in three areas: (1) determining which women should undergo endometrial biopsy, (2) analyzing the endometrium to detect polyps or submucosal

leiomyomas, and (3) assessing myometrial invasion from endometrial cancer (Fleischer, 1997b).

Transvaginal Sonographic Endometrial Evaluation

The clinical usefulness of sonography in women with postmenopausal bleeding relies on the ability to accurately measure endometrial thickness (see Chap. 8, Transvaginal Sonography). The thickest point along the endometrium from the anterior to posterior endometrial-myometrial junction is measured. In postmenopausal women with endometrial measurements of 5 mm or less, sonographic-pathologic studies have demonstrated that bleeding can be attributed to endometrial atrophy (Goldstein, 1990; Granberg, 1991). Endometrial hyperplasia, polyps, and carcinoma typically have thicker endometrial measurements.

A number of studies have been done to evaluate the capability of sonography to identify normal echostructural changes and pathology in the postmenopausal endometrium. For example, cystic endometrial changes implicate polyps, homogeneously thickened endometrium suggests hyperplasia, and a heterogeneous structural pattern prompts suspicion of malignancy. However, these sonographic findings show much overlap and cannot be used alone (Atri, 1994; Doubilet, 2000; Hulka, 1994; Levine, 1993). Additionally, Doppler studies of endometrial vasculature are not informative, because there are no significant differences between resistive and pulsatility indices in benign versus malignant causes of endometrial thickening (Bourne, 1995; Sheth, 1993).

Once diagnosed, determining the local extent of endometrial carcinoma is accurate using transvaginal sonography. Direct myometrial extension can be assessed; however, false-positive findings may be caused by compression and thinning of the myometrium from large benign lesions. In addition, color Doppler sonography of the myometrial vessels may help to identify invasive endometrial carcinoma. Although useful in evaluating the depth of myometrial invasion, sonography is *not* used to stage endometrial cancer because of its limited ability to evaluate disease beyond the corpus.

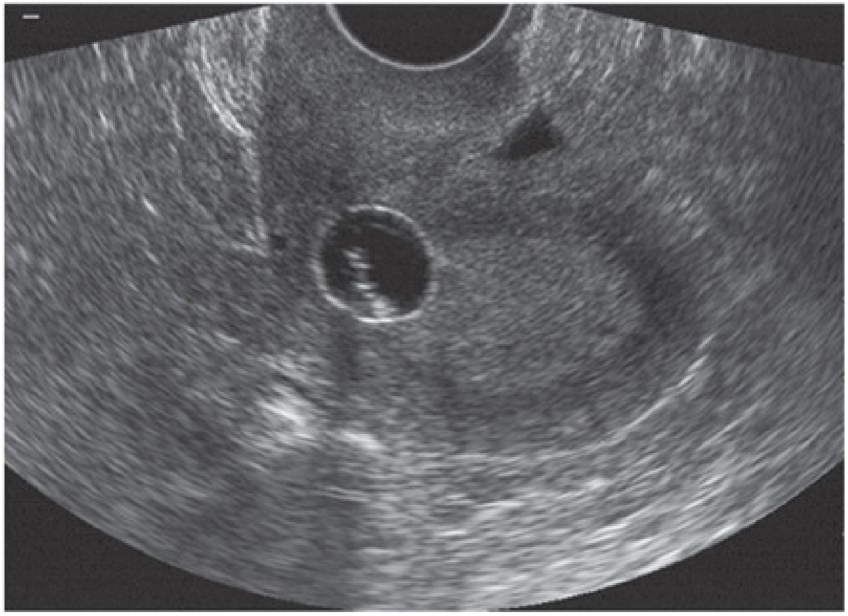
Saline-Infusion Sonographic Endometrial Evaluation

In addition to conventional TVS, SIS has also been used to evaluate the endometrium in various clinical situations (Lindheim, 2003a). Among others, these include abnormal uterine bleeding, clarification of endometrium thickening or other endometrial lesions, visualization of the endometrial stripe when poorly imaged because of uterine position or pathology, monitoring tamoxifen therapy, and some infertility investigations.

Defining Endometrial Lesions

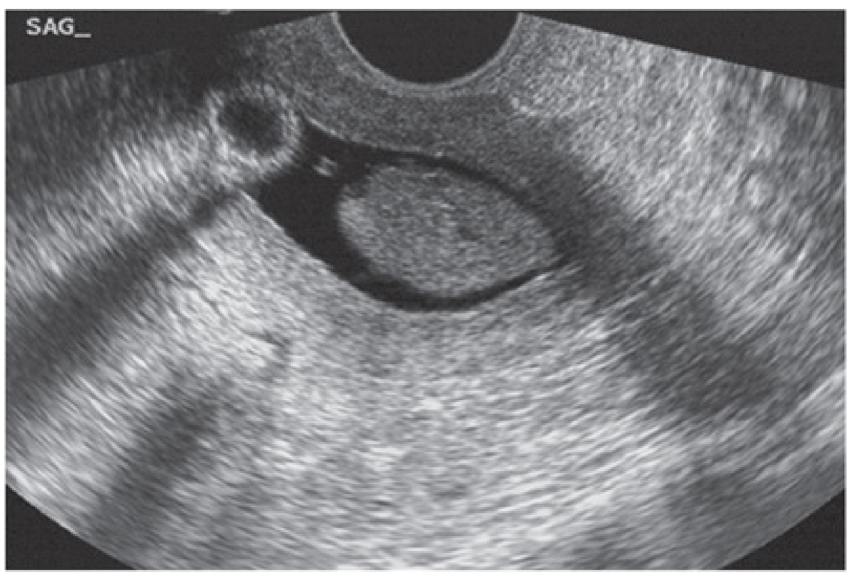
In further defining endometrial thickening, SIS is the best nonoperative procedure for diagnosing polyps (see Chap. 8, Saline-Infusion Sonography). The focal nature of these lesions is contrasted with the diffuse endometrial thickening seen with endometrial hyperplasia. Moreover, polyps and submucosal leiomyomas can often be differentiated based on two findings (Jorizzo, 2001). The first are differences in echotextureâ€”the leiomyoma is hypoechoic, similar to the myometrium, whereas the polyp is hyperechoic (Fig. 2-13). The second feature is demonstration of the endometrial mucosal surface, which divides the leiomyoma from the endometrial lumen (Jorizzo, 2001).

FIGURE 2-13



A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Endometrial polyp. **A.** Transvaginal sonogram of the endometrium after placement of the SIS balloon catheter (**arrow**). Note the homogenous-appearing thickened endometrium. **B.** Transvaginal SIS reveals the hyperechogenic polyp within the endometrial cavity. *(Courtesy of Dr. Elysia Moschos.)*

Obviously, SIS cannot be used to differentiate between benign lesions and malignancies with absolute certainty. Thus, many women with an endoluminal mass require histological evaluation to exclude malignancy (Dubinsky, 1999; Fleischer, 1997c; Jorizzo, 1999, 2001; Parsons, 1993).

Saline-infusion sonography is more accurate than either TVS or hysteroscopy to identify size, location, and depth of myometrial involvement of submucosal leiomyomas (Cicinelli, 1995). This is useful to predict outcomes and complications of hysteroscopic resection (Section 41-37, Hysteroscopic Myomectomy) (Bradley, 2000; Emanuel, 1995).

Monitoring Tamoxifen Therapy

In women taking tamoxifen, SIS is more useful than TVS. Saline-infusion sonography helps to delineate hyperplastic conditions in those women who have uterine bleeding when taking tamoxifen, whereas in the asymptomatic woman, SIS appears to add little value (Bertelli, 2000; Hann, 2001).

Evaluation of Infertility

Many infertility specialists are now incorporating SIS as a first-line screening tool for uterine evaluation before embryo transfer in women undergoing in vitro fertilization (IVF), ovum donation, and IVF-surrogacy (Kim, 1998; Lindheim, 1998; Serafini, 1998). In those with a history of recurrent abortion, SIS has been used to demonstrate not only mÃ¼llerian anomalies, but also a variety of other uterine cavity defects (Keltz, 1997). As a screening tool in this setting, it appears to be twice as accurate as hysterosalpingography and TVS (Soares, 2000).

Other Uses

Other diagnostic and therapeutic applications of SIS have been described. It may be used to locate a "lost" IUD and determine whether it is embedded in the myometrium (Bussey, 1996). It has been used to diagnose postabortal remnants, including placenta accreta, and to assess previous cesarean delivery scars (Monteagudo, 2001; Tal, 1997). Coccia and colleagues (2001) used pressure lavage under ultrasound guidance (PLUG) to treat intrauterine adhesions in seven women. This technique uses continuous accumulation of saline for the mechanical disruption of synechiae. Saline-infusion sonography can also guide direct biopsy of intrauterine pathology such as polyps (Bernard, 2002; Dubinsky, 2000; Lindheim, 2003b). Limitations primarily involve issues of technical feasibility, such as cervical stenosis or poor visualization due to leakage of saline with insertion of an operating instrument.

OVARY

Lesion Characterization

Sonography is commonly the initial and often the only imaging procedure performed in the evaluation of pelvic and ovarian masses. Simple cysts are one of the most common pelvic masses. The classic sonographic findings of simple cysts are smooth and regular margins, lack of internal echoes, and increased through-transmission or acoustic enhancement (see Fig. 2-1). Blood-filled cysts, such as hemorrhagic cysts and endometriomas, have variable appearances because of clot, lysis, and retraction. With these, internal echoes, septa, mural nodules, solid components, fluid-debris levels, and retracting clot can be seen. Some blood-filled cysts at first may appear to be solid, with an internal pattern of many small low-level echoes. However, consistent with a cyst, increased through-transmission is present (see Fig. 10-5). The sonographic characteristic that has been proven most important for the diagnosis of a hemorrhagic cyst versus an endometrioma is the change over time of its internal structure (see Fig. 9-11) (Derchi, 2001).

With ovarian neoplasms, some sonographic findings may be indicative. For example, a benign serous cystadenoma appears as a cystic mass containing clear fluid with thin internal septations. Mural nodules are infrequent. However, there is no clear boundary between the sonographic appearance of a cystadenoma and a cystadenocarcinoma. As a general rule, the greater the amount of solid tissue within the mass, the higher the probability of malignancy. Criteria suggesting cancer are presence of thick septations, multiple papillary projections, solid portions within the mass, and ascites (see Table 9-4). Mucinous cystadenomas usually are also cystic, and compared with their serous counterparts, they tend to have multiple internal septations, more echogenic fluid, and fluid-debris levels within the cyst.

Mature cystic teratomas (dermoid tumors) have a classical sonographic appearance (see Fig. 2-2). As described in Chapter 9, Mature Cystic Teratoma (Benign Cystic Teratoma or Dermoid Cyst), these include a markedly hyperechogenic mass with a structure similar to that of surrounding fatty tissue, cystic areas with round echogenic mural nodules, and calcifications, tufts of hair, and fat-fluid levels. These findings reflect the unique tissue contrasts found in these benign tumors.

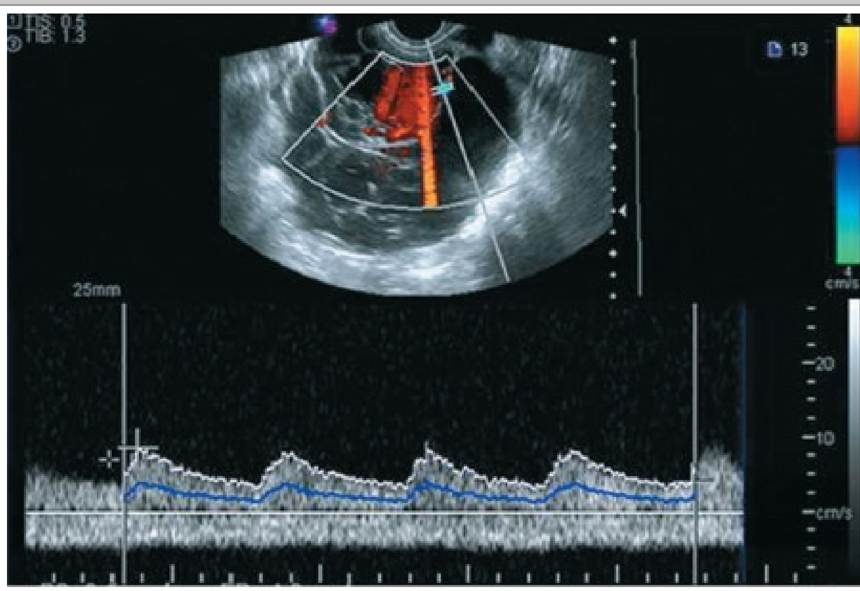
Malignant Characteristics

Sonography is the best diagnostic technique for preoperative determination of the malignant potential of an ovarian mass. To this end, scoring systems based on number and thickness of septa, presence and number of papillations, and proportion of solid tissue within the mass have been proposed to standardize the interpretation of findings (DePriest, 1993; Sassone, 1991). When morphology and structure of adnexal masses are combined with color Doppler and spectral analysis of flow signals, the specificity and positive predictive value of sonographic diagnosis is increased (Buy, 1996; Jain, 1994; Fleischer, 1993; Twickler, 1999). In a meta-analysis of 46 studies with 5,159 patients, Kinkel and colleagues (2000) reported significantly higher accuracy for combined sonographic techniques compared with that of each individual technique alone.

Neovascularity within a malignant neoplasm produces a significant increase in color Doppler flow signals. This assumption has led many investigators to evaluate presence, spatial distribution, and prevalence of flow signals within ovarian masses. Most malignant lesions appear well vascularized, with flow signals both in peripheral and central regions, whereas most benign tumors appear poorly vascularized. However, a firm diagnosis based on this alone is not possible. Indeed, both avascular malignant tumors as well as benign hypervascular masses have been reported (Brown, 1994; Kawai, 1992).

Neovascularity within malignancies is made up of abnormal vessels that lack smooth muscle and contain multiple arterio-venous shunts. Consequently, low-impedance flow is expected with such masses as shown in (Fig. 2-14) (Kurjak, 1992; Weiner, 1992). Other studies, however, demonstrated significant overlap between values from benign and malignant lesions (Jain, 1994; Levine, 1994; Stein, 1994).

FIGURE 2-14



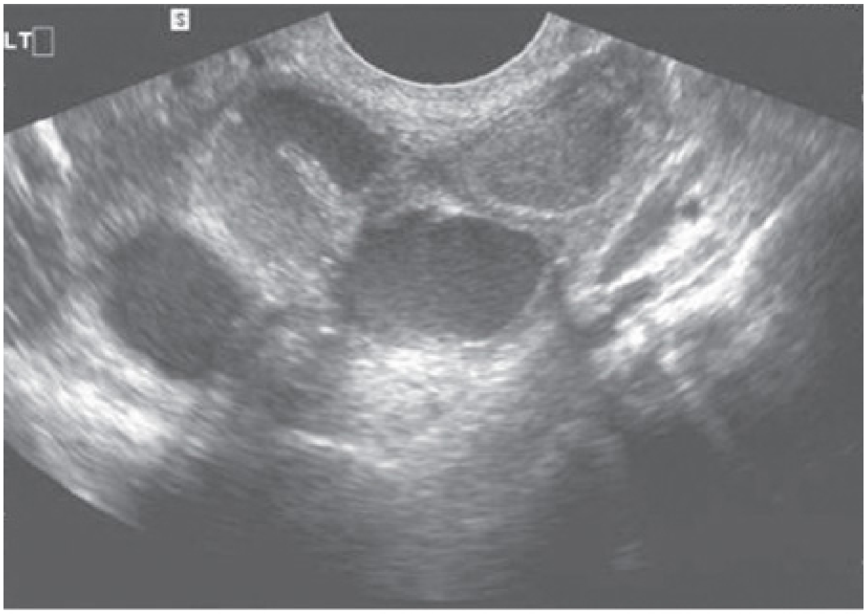
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Complex ovarian mass with irregular cystic areas demonstrating low-impedance [PI = 0.87] flow in a thick septum. This mass was found to be a mucinous cystadenocarcinoma at surgery. *(Courtesy of Dr. Elysia Moschos.)*

Torsion

In evaluation of other ovarian pathology, color Doppler can be employed to diagnose ovarian torsion. Its sonographic appearance varies according to the degree of vascular compromise and presence of an adnexal mass. Color Doppler of vessels in the infundibulopelvic ligament may aid the specific diagnosis by demonstrating absent arterial and venous flow (see Fig. 9-15). Importantly, central venous signals in tubo-ovarian torsion are thought to indicate ovarian tissue viability (Fleischer, 1995).

FIGURE 2-15



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Transvaginal sonogram in cross-section of an inflamed, dilated tube demonstrating thickened tubal walls, incomplete septa, and echogenic fluid. *(Courtesy of Dr. Elysia Moschos.)*

PELVIC INFLAMMATORY DISEASE

Acute Infection

Although pelvic sonography is commonly performed in women with acute salpingitis, there are no large studies evaluating its sensitivity, specificity, or overall usefulness (Boardman, 1997; Cacciatore, 1992; Patten, 1990). Sonographic findings vary according to disease. In early infection, sonography may be normal. With progression, early nonspecific findings include free pelvic fluid, endometrial thickening, endometrial cavity distension by fluid or gas, and indistinct borders of the uterus and ovaries. Enlarged ovaries with increased numbers of small cystsâ€"a so-called "polycystic ovary appearance"â€"has been shown to correlate with pelvic inflammatory disease (PID). Cacciatore and colleagues (1992) found larger-than-normal ovarian volumes in women with endometrial-biopsy or laparoscopically-proven PID. They also documented decreasing ovarian size with treatment.

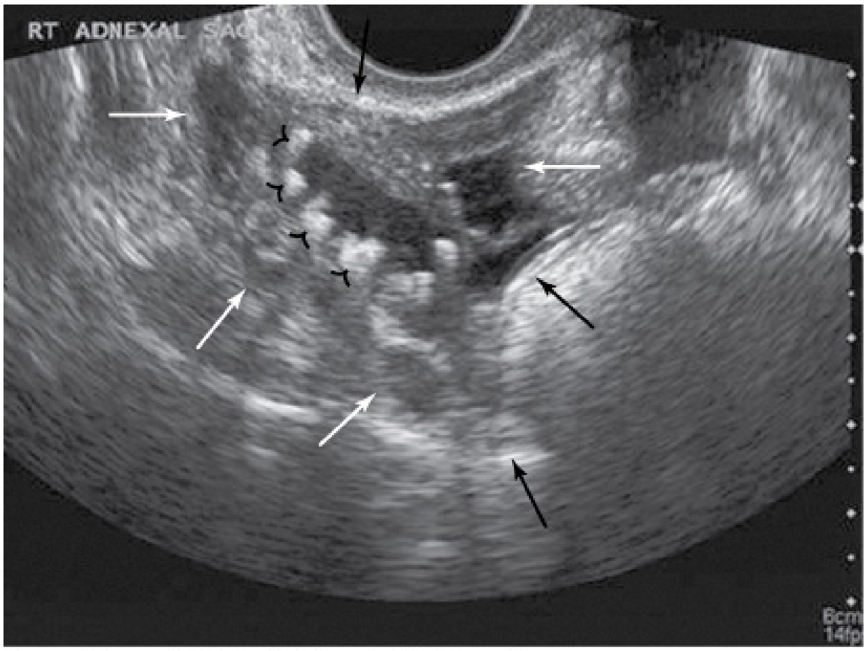
Sonographic findings of the fallopian tubes are the most striking and specific landmarks of PID (Fig. 2-15). Although normal tubes are rarely seen unless surrounded by ascites, an inflamed tube swells and the walls and endosalpingeal folds thicken, allowing visualization with sonography. As the lumen occludes distally, the tube distends and fills with fluid. A variety of appearances may result (Timor-Tritsch, 1998). The tube may become ovoid or pear shaped, filling with fluid that may be anechoic or echogenic. The tubal wall becomes thickened, measuring ≥5 mm, and incomplete septa-like structures are common as the tube folds back upon itself. If the distended tube is viewed in cross section it may demonstrate the cogwheel sign, due to thickened endosalpingeal folds (Timor-Tritsch, 1998). Typically the swollen fallopian tubes extend posteriorly into the cul-de-sac, rather than extending superiorly and anterior to the uterus as large ovarian tumors tend to do. Fluid-debris levels are often visualized in the dilated tubes and rarely, gas-fluid levels or echogenic bubbles of gas can be seen. Color and power Doppler show increased flow from hyperemia in

the walls, as well as incomplete septa of the inflamed tubes (Tinkanen, 1993).

Tubo-Ovarian Infection

As PID progresses, the ovary can become involved. When the ovary adheres to the tube, but is still visualized, it is called a *tubo-ovarian complex* . In contrast, a *tubo-ovarian abscess* is the result of a complete breakdown of ovarian and tubal architecture such that the separate structures are no longer identified (Fig. 2-16). If the contralateral side was not affected initially, it may become so. When both tubes are inflamed and occluded, the entire complex typically takes on a U-shape as it fills the cul-de-sac, extending from one adnexal region to the other (Horrow, 2004). The lateral and posterior uterine borders of the uterus become obscured and individual tubes and ovaries cannot be distinguished. In women not responding to medical therapy, sonography can be used to guide transvaginal drainage of these lesions (Kaakaji, 2000; Patten, 1990).

FIGURE 2-16



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

"Beads on a string" sign. The echogenic mural nodules shown here (**black carets**) within this tubo-ovarian abscess outlined by the **arrows** are thought to represent flattened and fibrotic endosalpingeal folds of the inflamed fallopian tube. *(Courtesy of Dr. Elysia Moschos.)*

Findings of Prior Infection

Findings of chronic PID include hydrosalpinx. Several sonographic findings such as its tubular shape, incomplete septa, and hyperechoic mural nodules can help to distinguish a hydrosalpinx from other cystic adnexal lesions (see Fig. 9-18). If color flow is detected in a hydrosalpinx, it tends to be less exuberant than flow seen in acute PID. Molander and colleagues (2002) found a higher pulsatility index in patients with a chronic hydrosalpinx (1.5 Â± 0.1) than with acute PID (0.84 Â± 0.04).

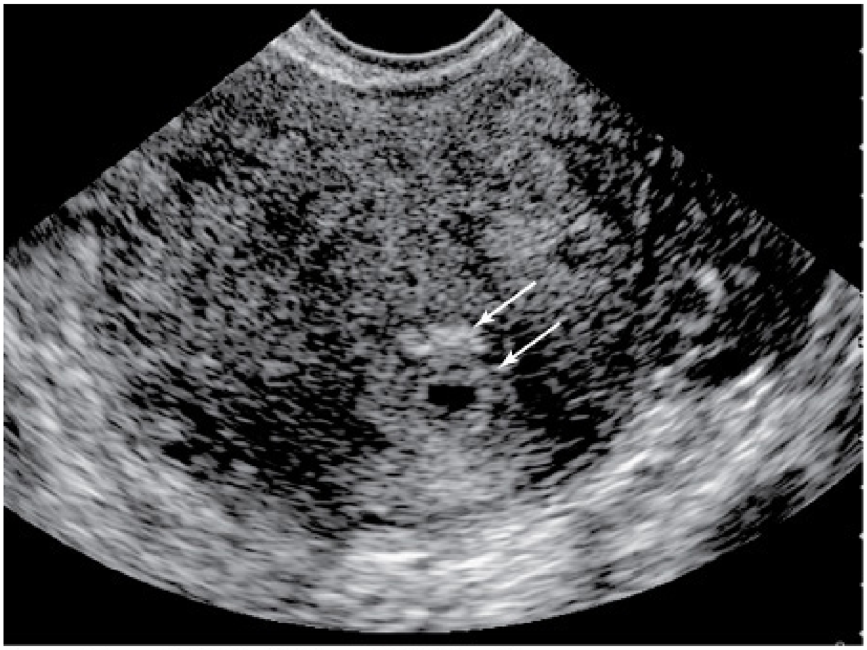
A small number of women with prior PID may have a peritoneal inclusion cyst. This diagnosis is made when the ovary is surrounded by a loculated fluid collection with thin septations (Horrow, 2002). A peritoneal inclusion cyst forms when fluid from a ruptured ovarian cyst is trapped around the ovary by adhesions.

ECTOPIC PREGNANCY

Sonography plays a pivotal role in clinical management of suspected ectopic pregnancy. Because a simultaneous uterine and ectopic pregnancyâ€”a heterotopic pregnancyâ€”is rare, identification of a uterine pregnancy is the single most important finding

for exclusion of an ectopic gestation. Intrauterine pregnancy can be assured if a gestational sac, double-decidual sign, or embryo is found within the endometrial cavity. All pregnancies can induce an endometrial decidual reaction, but a double decidual signâ€”two echogenic external layers encircling the anechoic gestational sacâ€”is caused by invasion of the decidua parietalis and decidua capsularis of the developing placenta (Fig. 2-17).

FIGURE 2-17



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Transvaginal sonogram demonstrating a double decidual sign. The two concentric echogenic layers surrounding the anechoic gestational sac are the result of the inner decidua capsularis (**arrow**) and the peripheral decidual parietalis (**arrow**). *(Courtesy of Dr. Elysia Moschos.)*

Ectopic pregnancy may present with a large variety of sonographic patterns (see Fig. 7-5). An extrauterine gestational sac containing an embryo is an unequivocal finding; however, solid and complex adnexal masses in conjunction with an empty uterus and a positive pregnancy test result are frequently encountered. A complex adnexal mass is usually caused by hemorrhage within the ectopic sac, or by an ectopic pregnancy that has ruptured into the tube. Complex free fluid or blood clots are often associated (Filly, 1987; Fleischer, 1990; Nyberg, 1987). Placental blood flow within the periphery of the complex adnexal massâ€”the ring of fireâ€”can be seen with transvaginal color Doppler imaging (see Fig. 7-7). Although this can aid in the diagnosis, this finding can also be seen with a corpus luteum of pregnancy (Pellerito, 1992b).

GESTATIONAL TROPHOBLASTIC DISEASE

Sonography plays an important role in establishing the diagnosis of hydatidiform mole. A complete hydatidiform mole displays tissue that is interspersed with numerous punctate sonolucencies (Fig. 37-4). The appearance varies according to gestational duration and correlates with the size of hydropic villi (Jones, 1975). For example, molar pregnancies of menstrual age from 8 to 12 weeks typically appear as homogenously echogenic intraluminal tissue, and villi have a maximum diameter of 2 mm. With maturation, vesicles may approach 10 mm in diameter, and they are readily seen as sonolucent cystic spaces. These villi create a classic transabdominal image termed a "snowstorm" pattern. Fetal tissues and amniotic membranes are absent.

In contrast, features of a partial mole include hydropic placental degeneration and presence of concomitant fetus or fetal parts. Unfortunately, hydropic placental degeneration may give a similar sonographic appearance as hydatidiform molar tissue (Fleischer, 2001). Villi are swollen and edematous. These hydropic changes are seen sonographically in 20 to 40 percent of placentas from

aborted pregnancies (Reid, 1983). Thus, histologic, genetic, and immunologic analysis of tissue is typically required to differentiate between molar and nonmolar pregnancy (see Chap. 37, Immunostaining).

Theca-lutein cysts that enlarge under the influence of high serum levels of β-hCG are also commonly seen with molar pregnancies. They are typically bilateral and appear as multiloculated cystic masses that measure between 4 and 8 cm in diameter (Fleischer, 2001).

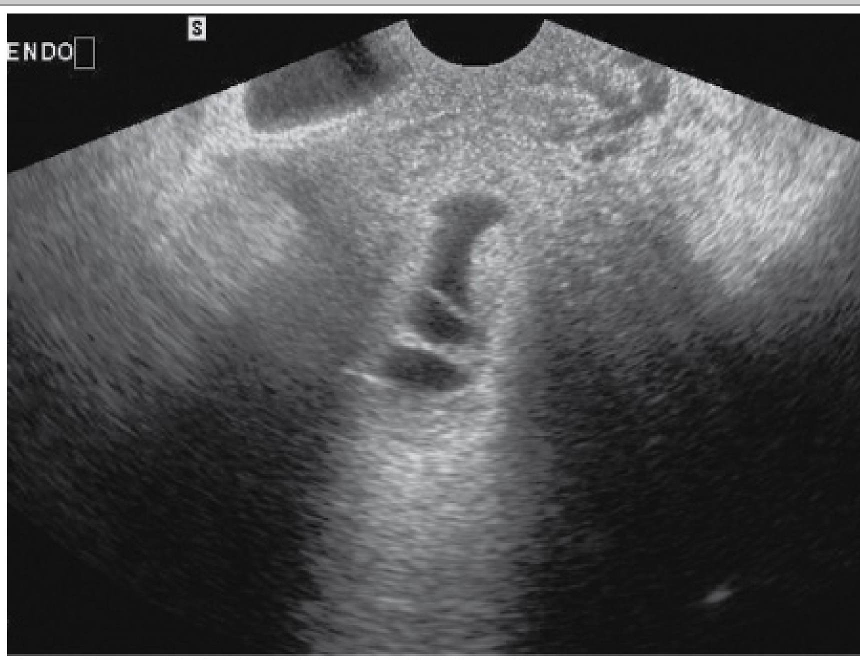
Sonography may also be used to assess possible invasive trophoblastic disease (Taylor, 1987). The sonographic appearance of invasive trophoblastic tissue is that of a focal irregular echogenic region within the myometrium. Doppler sonography can display the presence and relative aggressiveness of myometrial implants by depicting increased and typically turbulent flow to these tumors through the uterine arteries (Taylor, 1987). Sonography and Doppler analysis are also used to evaluate tumor response to chemotherapy (Hammond, 1980). Moreover, evaluation of the liver and kidney for metastatic disease may be aided by sonography (Munyer, 1981).

INFERTILITY

Sonography is employed for four main purposes in the approach to female infertility: (1) identification of abnormal pelvic anatomy; (2) detection of pathology causal or contributory to infertility; (3) evaluation of cyclic physiologic uterine and ovarian changes; and (4) surveillance and visual guidance during infertility treatment (Barnhart, 2000; Parsons, 2001).

Sonography can easily demonstrate anatomic uterine defects that may affect both gamete passage and ovum implantation. As discussed, conventional TVS can be used to visualize submucous leiomyomas and polyps; however, relationships of these lesions with the endometrial surface is better seen with SIS. Intrauterine synechiae, which can be seen as hypoechoic lines disrupting the echogenic endometrium by conventional sonography, are more definitively seen during SIS as echogenic bands extending from one endometrial surface to the other (Fig. 2-18). In addition, transvaginal sonography is used initially to detect congenital uterine anomalies that cause infertility or early spontaneous abortion. Thereafter, MR imaging is used to characterize and evaluate mÃ¼llerian anomalies. A complete description of these anomalies is found in Incidence and Classification.

FIGURE 2-18

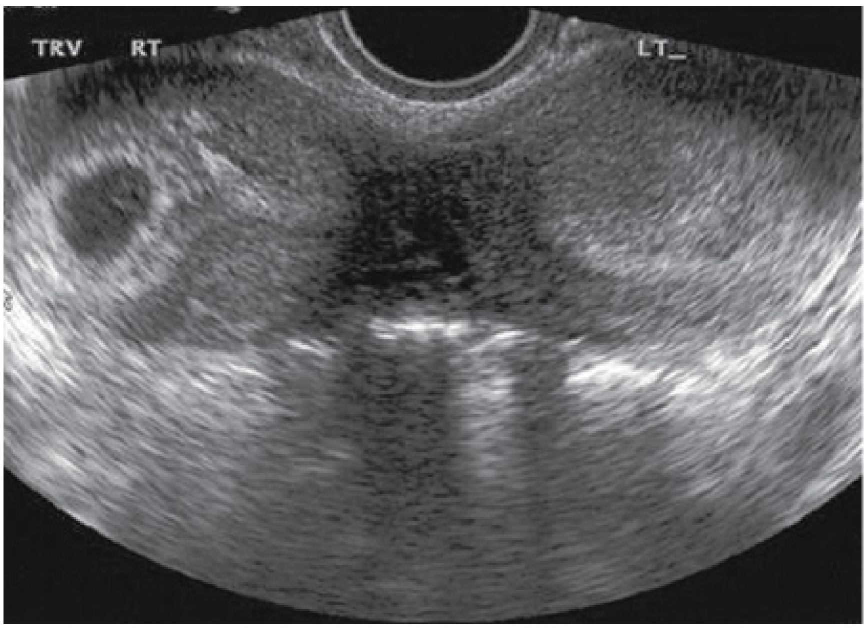


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Asherman syndrome. Transvaginal saline-infusion sonography demonstrates the echogenic intrauterine synechiae. *(Courtesy of Dr. Elysia Moschos.)*

In women with complex anomalies associated with vaginal agenesis or imperforate hymen, hematocolpos is commonly seen, often with associated hematometra or hematosalpinx (Hall, 1994). A complete duplication anomaly, such as uterus didelphys, can be accurately diagnosed by sonography with the imaging of two separate and divergent uterine horns that have a deep fundal cleft between the two hemi-uteri and a wide angle between the two endometrial cavities (Fig. 2-19). The differentiation between a bicornuate and septate uterine anomaly is less confidently achieved by traditional transvaginal sonographic techniques. Ideally, measurement of the angle between the two endometrial cavities and analysis of the fundal shape helps to differentiate between a bicornuate uterus (angle ≥ 105Â°) and a septate uterus (angle ≤ 75Â°) (Reuter, 1989). Combining TVS findings with SIS provides accuracy up to 90 percent to distinguish the two anomalies. Three-dimensional sonography is considered by some to be the best noninvasive method for distinguishing between these uterine anomalies (Kupesic, 2001).

FIGURE 2-19



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Uterus didelphys. Transvaginal sonogram in the transverse plane best depicts the two completely separate uterine horns. A gestational sac is evident in the right uterus. *(Courtesy of Dr. Elysia Moschos.)*

A unicornuate uterus, however, is difficult to recognize sonographically. The dilated rudimentary horn is often misdiagnosed as a uterine or adnexal mass (Hall, 1994). Complete evaluation of these cases requires MR imaging. With any uterine anomaly, especially if unilateral, proper positioning of the kidneys should be documented because of increased associated genitourinary anomalies.

Pelvic endometriosis is another frequent cause of infertility. Sonography is the most common imaging procedure to evaluate suspected endometriosis, although its role is mostly limited to evaluation of endometriotic cysts. Its capability in the detecting small implants and adhesions is limited. Endometriomas exhibit a variety of sonographic appearances, the most common being a cystic pelvic mass with a thick wall and an internal structure made of diffuse low-level echoes (see Fig. 10-5). Magnetic resonance imaging has been proven to be more specific than sonography for identifying endometriomas, and thus it is indicated in difficult cases (see Fig. 10-6).

One of the most powerful uses of sonography in the infertile patient is surveillance of various treatment techniques. Sonography is used to monitor folliculogenesis both in normal and stimulated cycles. In natural cycles, observation of a developing follicle and prediction of ovulation allow optimal timing of procedures such as post coital testing, human chorionic gonadotropin (hCG) administration, intercourse, insemination, and ovum collection. At ovulation, the follicle usually disappears and fluid is observed in the cul-de-sac of Douglas. At the follicular site, the corpus luteum appears as an irregular structure containing a small quantity of fluid, internal echoes, and a thick wall (Dill-Macky, 2000). In stimulated cycles, sonographic detection of too many follicles allows withholding hCG induction to prevent ovarian hyperstimulation syndrome. If this develops, sonography is used to grade disease severity through measurements of ovarian size, detection of ascites, and analysis of renal flow resistances (Fig. 20-5). (Barnhart, 2000; Parsons, 2001). Blood flow in the ovulating ovary decreases throughout the menstrual cycle. At ovulation, there is a dramatic increase of blood flow velocities in vessels surrounding the corpus luteum because of angiogenesis with low-impedance waveforms. In women undergoing in vitro fertilization, low ovarian vessel impedance may correlate directly with pregnancy rates (Baber, 1988). Lastly, sonography can be used to guide interventional maneuvers such as oocyte retrieval and transfer of embryos into the endometrial cavity (Fig. 20-12).

Sonosalpingography

Until recently, a fallopian tube could be detected with sonography only when distended by fluid, such as in cases of obstruction. Injection of echogenic contrast material under real-time sonography, called *sonosalpingography* or *sonohysterosalpingography* , is proposed as a means to assess tubal patency without the need for HSG. It can be performed in an outpatient setting, has good patient acceptance, and it is almost as accurate as HSG (Campbell, 1994; Lerner, 1997).

Sonosalpingography is done in a manner similar to SIS. Fluid egress from the uterine cavity is blocked by a balloon catheter within the cervical canal. The approximate location of the fallopian tubes as they insert into the uterine cornua is identified with the transvaginal probe. Tubal patency is confirmed by visualizing passage of saline through the tubes, which is detected by means of color or pulsed Doppler techniques (Kupesic, 1997). A 90-percent correlation with traditional techniques has been reported by many (Allahbadia, 1992; Campbell, 1994; Schlief, 1991; Stern, 1992).

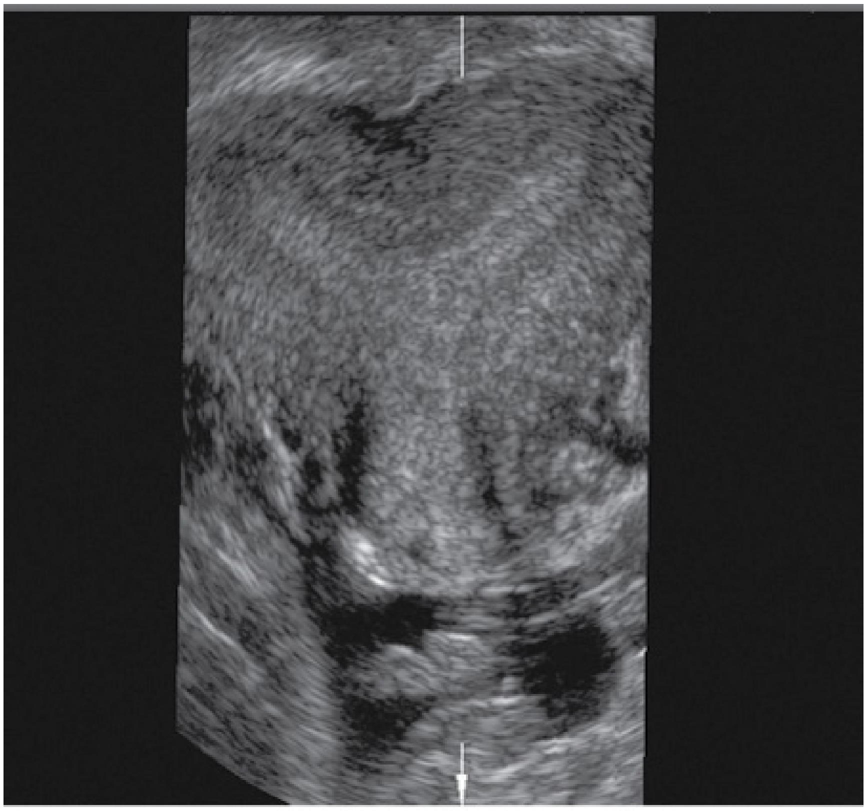
However, a patent tube does not always correlate with a normally functioning tube. Thus, HSG may still be needed for more accurate delineation of the tubal anatomy for selected indications.

Three-Dimensional Sonography

Sonogram images shown on a monitor screen are two-dimensional (2-D). Anatomic parts, however, are inherently three-dimensional (3-D). New scanners allow collection of 3-D data and represent it on a two-dimensional screen (Kurjak, 2001). Thus, 3-D techniques overcome the limitations of conventional 2-D sonography by allowing a more detailed assessment of morphology, with no restriction of number and orientation of scanning planes (Aruh, 1997; Umek, 2002).

Three-dimensional sonography has recently been used in clinical practice, especially obstetrics. In gynecology, it is useful in the assessment of complex ovarian masses, uterine anomalies, evaluation of the uterine cavity, and diagnosis of interstitial pregnancies (Fig. 2-20) (Izquierdo, 2003).

FIGURE 2-20



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Arcuate uterus. The coronal plane of 3-dimensional sonography best illustrates this normal uterine variant. *(Courtesy of Dr. Elysia Moschos and Dr. Diane Twickler.)*

There have been variable results concerning the role of 3-D transvaginal sonography with respect to its sensitivity and specificity in detecting malignancies in adnexal masses (Alcazar, 2003). There is agreement that 3-D sonography allows a more detailed assessment of the internal structure of ovarian masses. Moreover, the addition of color Doppler to 3-D evaluation allows display of the internal architecture of neovascularization, also characteristic of malignant neoplasms (Kurjak, 2001).

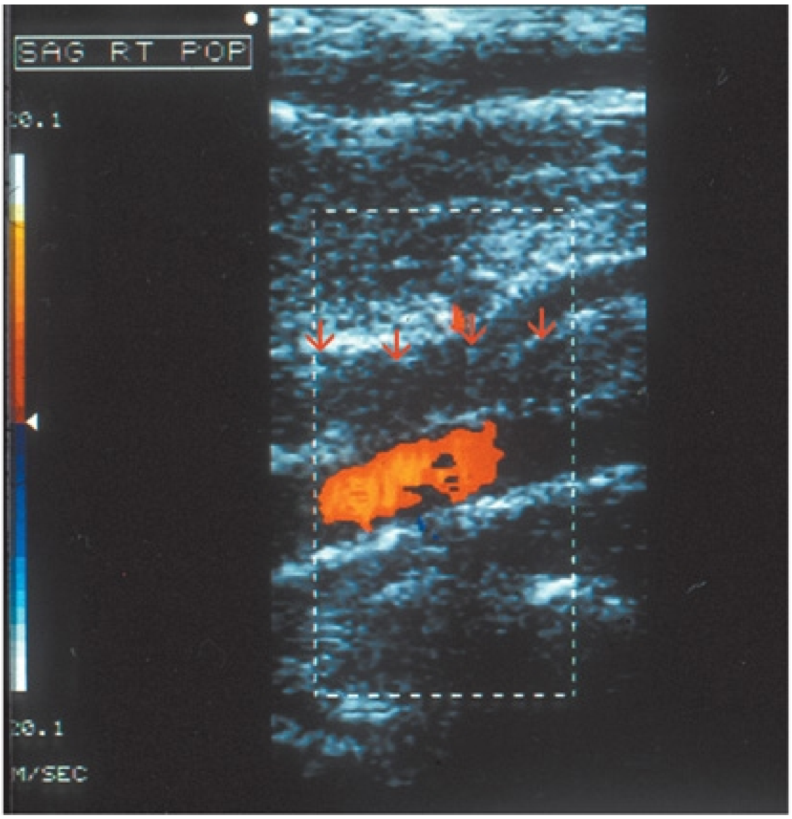
A number of investigators have described 3-D sonography with image reconstruction for evaluation of congenital mÃ¼llerian anomalies (Jurkovic, 1995; Raga, 1996; Steiner, 1994). It provides detailed images of both the internal shape of the endometrial cavity as well as the external contour of the fundus. Thus, various types of mÃ¼llerian anomalies can be differentiated because the uterine horns and fundal contour can be displayed clearly in the same plane. Importantly, the information obtained from 3-D imaging can provide helpful details for preoperative planning and may even help predict the likely outcome of metroplasty (Wu, 1993).

Using 3-D technology, it is possible to generate endometrial cavity images that allow better definition and characterization of focal endometrial thickenings, such as polyps, hyperplasia, and cancer. In their comparative study of 36 women with postmenopausal bleeding, Bonilla-Musoles and associates (1997) compared results from 3-D SIS with findings from TVS, transvaginal SIS, transvaginal color Doppler, and hysteroscopy. Visualization of the uterine cavity and endometrial thickness with 3-D SIS was comparable to hysteroscopy and better than with the other sonographic techniques.

Compression Sonography of Lower Extremities

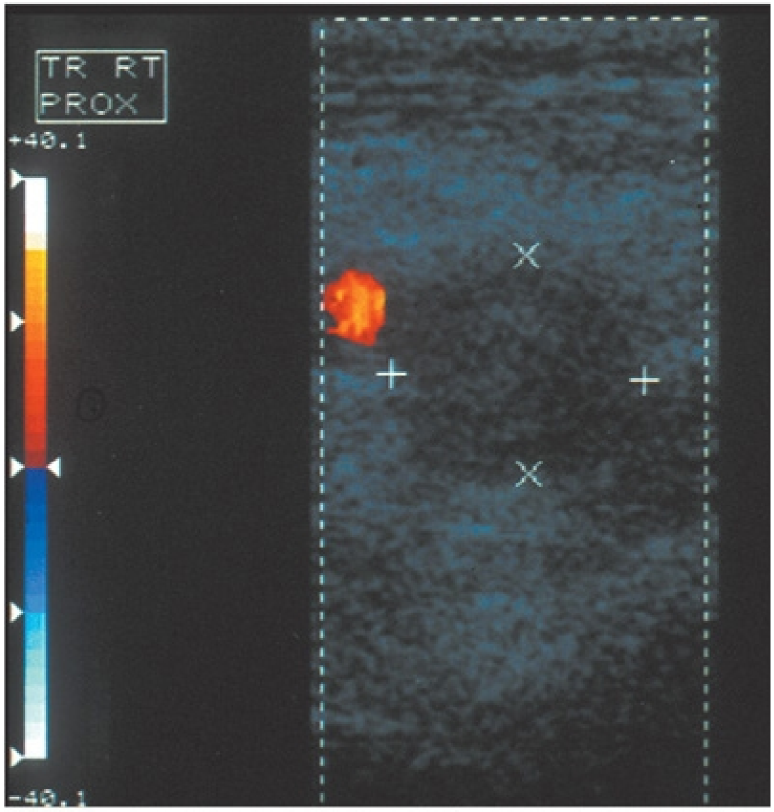
Compression sonography, often combined with color Doppler sonography, is the initial test currently used to detect deep venous thrombosis (see Fig. 39-4) (Greer, 2003). Sonographic evaluation of leg veins is divided into three parts: (1) the groin and thigh are examined with the patient supine; (2) the popliteal region is examined with the patient lying on her side or sitting; and finally, (3) the calf veins are examined with the patient sitting. The diagnosis of thrombosis is based on impaired visibility, noncompressibility, and typical echo pattern of a thrombosed vein (Fig. 2-21). In symptomatic patients, examination of the femoral, popliteal, and calf trifurcation veins is more than 90-percent sensitive and over 99-percent specific for proximal thrombosis (Davis, 2001; Schellong, 2004). It has a negative predictive value of 98 percent (American College of Obstetricians and Gynecologists, 2000a, 2000b). Although useful for proximal occlusions, compression sonography is significantly less reliable for detecting calf vein thromboses (Bates, 2004).

FIGURE 2-21



A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Sagittal (**A**) and transverse (**B**) images from a lower extremity. Color Doppler ultrasound study in a woman with popliteal vein thrombosis. **A.** Red arrows demarcate the popliteal vein with no flow suggesting clot in the lumen, which sits above the artery demonstrating normal flow as evidenced by the red color map. **B.** The transverse image shows the large size of the vein due to the thrombus (**cursors**), as well as normal flow in the artery, evidenced by the red color map. *(Courtesy of Dr. Diane Twickler.)*

Lensing and colleagues (1989) compared contrast venography with real-time sonography in 220 patients. They found that both the common femoral and popliteal veins were fully compressibleâ€”no thrombosisâ€”in 142 of 143 patients who had a normal venogram (99-percent specific). All 66 patients with proximal vein thrombosis had noncompressible femoral or popliteal veins, or both (100-percent sensitive). Importantly, normal venous sonography findings do not necessarily exclude pulmonary embolism because the thrombosis may have already embolized or because it arose from deep pelvic veins inaccessible to sonographic evaluation (Goldhaber, 2004).

RADIOGRAPHY

Plain radiographs are used in gynecologic practice in a manner similar to other medical specialties. Plain films include radiographs of the chest and abdomen. Some plain radiographs are used to evaluate women with gynecologic malignancies (Soper, 2001). Examples are chest radiographs to screen for pulmonary metastases during malignancy staging, including gestational trophoblastic disease, and for surveillance after initial treatment. A number of specialized radiographic procedures are especially useful or are specific to evaluation of gynecologic conditions.

Intravenous Pyelography

Excretory urography, or intravenous pyelography (IVP), is a radiographic study which provides imaging of the urinary tract. Comparing CT and sonography, CT images show more detail of pelvicalyceal and ureteric anatomy, but provides less information

about the renal parenchyma and bladder (Webb, 2001).

After an initial plain radiograph, termed a scout film, delineates urinary calculi, intravenous contrast agent is given. Immediately thereafter, the concentrating function of the proximal tubules renders the renal parenchyma radiodenseâ€”in the nephrogram phaseâ€”and allows evaluation of renal size, contour, and axis. A radiograph obtained after 5 minutes depicts contrast excreted into the collecting systemâ€—the pyelogram phaseâ€—and the collecting system is evaluated for symmetry and promptness of excretion. A final postvoiding radiograph completes the evaluation.

Many preoperative pyelograms performed in the past have been supplemented by sonography and spiral CT imaging. For example, most clinicians in the United States have substituted CT imaging in cervical cancer staging because it allows visualization of the cervix, parametria, uterus, adnexa, retroperitoneal lymph nodes, liver, and ureters (International Federation of Gynecology and Obstetrics [FIGO] Committee on Gynecologic Oncology, 1998). However, a preoperative IVP is often used for suspected urinary anomalies in women with a reproductive tract anomaly. It is also indicated to confirm lower urinary tract patency in the setting of pelvic neoplasm, such as a large cervical or pelvic mass that is fixed and adherent to the pelvic side wall or that causes urinary symptoms.

As many as 5 to 10 percent of women have an allergic reaction to iodide during IVP, and 1 to 2 percent of these reactions is life-threatening. Pretreatment with oral corticosteroids has significantly reduced the incidence of allergic reactions (Lasser, 1987). Moreover, nonionic iodinated contrast media agents have a 5- to 30-fold decreased incidence of allergic reactions, but are more expensive than traditional ionic contrast media (Mishell, 1997).

There also may be significant nephrotoxicity due to hyperosmolar ionic contrast, which is believed to cause direct tubular insult and ischemic injury. Women with diabetes, renal impairment, and congestive heart failure are at high risk for contrast nephrotoxicity. Thus, low osmotic, nonionic contrast materials are less nephrotoxic and should be considered in special cases such as these (Mishell, 1997).

Voiding Cystourethrography and Positive Pressure Urethrography

These radiographic procedures are commonly used imaging methods to evaluate the female urethra and are discussed in detail in Chapter 26, Voiding Cystourethrogram. In addition, recent studies have demonstrated that MR imaging is an excellent modality for visualizing urethral diverticula and that it is more sensitive than voiding cystourethrography for delineating diverticula with complex structures (Neitlich, 1998; Daneshgari, 1999).

Hysterosalpingography

This radiographic imaging technique is used to evaluate the endocervical canal, endometrial cavity, and the lumina and patency of the fallopian tubes by injecting radiopaque contrast material through the cervical canal (see Chap. 19, Hysterosalpingography). Used primarily in evaluation of infertility, an average HSG is performed in 10 minutes, involves approximately 90 seconds of fluoroscopic time, and has an average radiation exposure to the ovaries of 1 to 2 rads.

Hysterosalpingography is performed between cycle days 5 and 10, following cessation of menstrual flow to minimize infection and the risk of flushing an ovum from the fallopian tube. The test causes cramping and a nonsteroidal anti-inflammatory drug taken 30 minutes prior to the procedure may minimize discomfort. An acorn cannula, pediatric Foley catheter, or designated injection catheter is introduced just inside the external cervical os and contrast media is injected. A paracervical block may be indicated in selected patients, such as those with cervical stenosis. Because rapid injection may cause tubal spasm, a slow injection of usually no more than 3 to 4 mL of media allows a clear outline of the uterine cavity. Generally, only three radiographic views are neededâ€—a preliminary view before injecting contrast, a view showing fill of the uterine cavity, and a third demonstrating spill of contrast from the tubes into the peritoneal cavity.

There are many variations in the appearance of a normal HSG (see Fig. 19-5). The endometrial cavity is usually triangular or sometimes T-shaped in the anteroposterior projection. In the lateral view it is oblong. The contour of the endometrium is usually smooth. It occasionally appears to have polypoid-filling defects that can be isolated or diffuse, and can be difficult to distinguish from endometrial polyps or hyperplasia (Lindheim, 2003a). Inadvertent injection of air bubbles introduces artifact.

Contraindications to HSG include acute pelvic infection, active uterine bleeding, pregnancy, and iodine allergy. Complications of HSG are rare but can be serious. The overall risk of acute pelvic infection serious enough to require hospitalization is less than 1 percent, but may be up to 3 percent in women with prior pelvic infection (Stumpf, 1980). Because of serious morbidity, routine prophylaxis is given with doxycycline orally, 100 mg twice daily, beginning the day before HSG and continued for 2 more days thereafter. In addition, pelvic pain, uterine perforation, and vasovagal reactions may occur. Complications from the contrast include allergic reactions and entry into the vascular system with high injection pressures. Embolic phenomena, pelvic peritonitis, and granuloma formation with oil-based contrast agents are rare.

Selective Salpingography

In some cases, it is not possible to distinguish whether a tubal blockage seen by HSG is caused by anatomic occlusion or tubal spasm. Hysteroscopic tubal cannulation can further clarify and treat many cases of proximal tubal occlusion as described in Hysteroscopic Proximal Fallopian Tube Cannulation. Alternatively, transcervical selective salpingography and tubal catheterization (SS-TC) under fluoroscopic guidance is another procedure that may be used. It is performed during the follicular phase of the cycle with the catheter forwarded through the cervix and advanced by tactile sensation to the tubal ostium. The position of the catheter is checked fluoroscopically and if satisfactory, water- or oil-soluble contrast is injected. If the obstruction is overcome, the tubal contour is outlined with contrast agent. If the proximal tubal obstruction persists, a guidewire is threaded through the inner cannula of the catheter and advanced toward the obstruction and gently manipulated to overcome the blockage. The guidewire is then withdrawn, and contrast medium is injected through the catheter to confirm patency. This fluoroscopic tool is effective at diagnosing and treating proximal tubal blockage (Capitanio, 1991; Ferraiolo, 1995; Thurmond, 1991; Woolcott, 1997).

Bone Densitometry

Depending on its mineral density, bone absorbs x-rays to different degrees. Although plain radiography is useful in the initial evaluation of osteopenia and osteoporosis, it is not sensitive enough to assess bone density. Other techniques are accurate, sensitive, and safe to quantify severity of bone loss and serve as a baseline for evaluating therapeutic benefits (Kaplan, 1995). Most measurements of bone density provide site-specific information about the time-specific quantity of bone, but do not assess either current or past rates of bone remodeling. Sequential density measurements are therefore necessary to assess the rate of bone loss (Kaplan, 1995).

Currently, two methods used commonly are dual-energy x-ray absorptiometry (DEXA) to assess integral bone mineralâ€”cortical and trabecularâ€”density in the hip and spine, and quantitative computed tomography (QCT) to evaluate bone mineral in high-turnover trabecular bone.

Of these, DEXA is the best technique for assessment of axial osteopenia (see Fig. 21-10). It employs two x-ray beams of different energy levels and accurately measures bone density in the hip and spineâ€”areas most vulnerable to osteoporotic fractures. The spine is commonly scanned between the first and fourth lumbar vertebrae Measurements with DEXA are precise and accurate, radiation dose is lowâ€”less than 5 mrem, and patient acceptability is high because the procedure time is usually only 5 to 15 minutes (Jergas, 1993). Although DEXA instruments that measure bone mass at peripheral sites such as in the forearm are also available, these may not predict hip fractures as accurately as direct hip measurement. One disadvantage of DEXA is that bone spurs, aortic calcifications, and arthritis may falsely elevate reported bone density.

In contrast, QCT uses either x-rays or gamma rays to provide a cross-sectional view of the vertebral body. As the rate of turnover in trabecular bone is nearly eight times that in cortical bone, this technique detects early metabolic changes in a highly vulnerable region. Its precision is excellent but may be reduced with severe osteopenia and kyphosis, with increased fat content from obesity or fatty bone marrow in older patients, and by the technical aspects of positioning (Kaplan, 1995; Miller, 1999).

Another technique, which has not been validated, is quantitative sonography (Pejovic, 1999). This may provide information about the structural organization of bone (World Health Organization [WHO] Study Group, 1994; American Association of Endocrinologists, 1996). Small portable ultrasound units are available for rapid measurement of heel bone mass in the office, with readings made in 10 seconds.

Uterine Artery Embolization

This is a definitive independent treatment of uterine leiomyomas that was first introduced in the early 1990s. Uterine artery embolization (UAE) is a radiologic procedure that uses angiography to visualize blood circulation and is discussed fully in Chapter 9, Uterine Artery Embolization. Primarily, flow through the uterine arteries is stopped, resulting in leiomyoma ischemia and necrosis.

COMPUTED TOMOGRAPHY

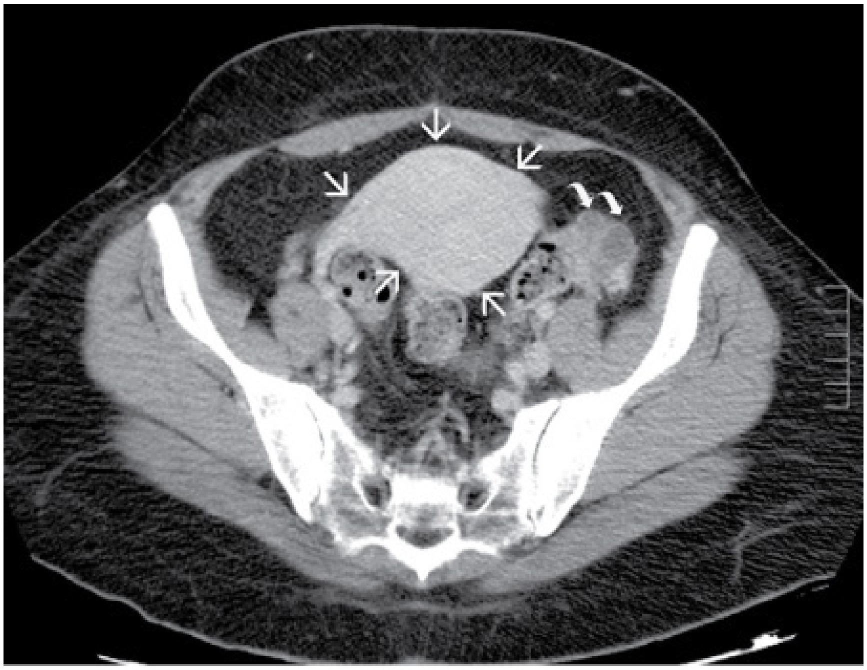
This procedure involves multiple exposures of thin x-ray beams, which are translated into two-dimensional axial images of the particular area of interest, termed a *slice* . Multiple slices of the target body part are obtained along its length. Multiple-channel helical computed tomography, also called spiral CT, allows for continuous acquisition of images in a spiral with the potential for image reformatting in multiple planes. This technique is much faster and allows for images to be manipulated for analysis after they have been acquired.

Many variables affect radiation dose, especially slice thickness and number of cuts obtained. If a study is performed with contrast, twice as many images will be obtained, and the target area radiation dose is therefore doubled.

Normal Anatomy with Computed Tomography

The uterus is identified as a homogenous, soft tissue oval or triangular structure situated posterior to the bladder (Fig. 2-22). The uterine walls enhance after intravenous contrast medium. Unlike sonography and MR imaging, the endometrium is not identifiable on CT imaging. The smooth lateral margins of the cervix are well defined because of contrast with adjacent parametrial fat. There is uniform enhancement of the cervix after intravenous contrast medium. The endocervical canal, which can be identified by MR imaging, cannot be distinguished by CT imaging. Images of the vagina and vulva are strongly enhanced by contrast medium (Constant, 1989). Typically, the ovaries are relatively hypodense, variable in appearance and position, and usually situated posterolateral to the uterus (Friedman, 1992).

FIGURE 2-22



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Computed tomography (CT) of the female pelvis in the axial plane demonstrates the normal uterus (**arrows**) as well as cysts in the left ovary (**curved arrows**). *(Courtesy of Dr. Diane Twickler.)*

The parametria can be well visualized with CT imaging, and thus it is useful for gynecologic malignancies. The parametria consist of a large proportion of fatty tissue, but contain some soft tissue representing fibrous tissue, blood vessels, and lymphatics. The cardinal ligaments are seen on axial scans as triangular structures of soft tissue extending from the lateral borders of the cervix and upper vagina to fuse with the deep fascia covering the levator ani. The round ligaments can be identified in the upper margin of the parametria, extending anterolaterally toward the inguinal ring (Friedman, 1992). The uterosacral ligaments are easily identified on axial and coronal views, passing from the lateral margins of the cervix and vaginal fornices to the sacrum. Finally, the ureter and the uterine arteries can be identified within the broad ligament (Constant, 1989).

Gynecologic Malignancy

In most instances, sonography is the preferred initial method of evaluating the female pelvis (Fleischer, 1989; O'Brien, 1984). With pelvic pathology, MR imaging is now often preferable to CT imaging because it does not use radiation and provides excellent views of pelvic structures in multiple planes (Carr, 2002). For these reasons, there is a relative paucity of literature concerning CT images of benign pelvic disorders.

However, CT imaging is probably the most frequently used imaging technique for the evaluation and surveillance of gynecologic malignancies (Soper, 2001). Oral and rectal contrast allows visualization of the gastrointestinal tract, whereas intravenous contrast enhances visualization of blood vessels and viscera. Rapid resolution CT imaging have much greater sensitivity than techniques used previously and can be used to detect 2- to 3-mm lesions in the lungs and solid viscera (see Fig. 37-8). Scans with contrast yield high-quality information about retroperitoneal lymph nodes and ureters. Spiral CT scans record images during arterial, capillary, and venous phases of tissue enhancement during contrast administration. This allows improved imaging of small vessels and tissue interfaces within the visceral parenchyma. Whereas sensitivity for small intraperitoneal metastases is limited, CT scans can give a useful estimate of the location of bulky metastases, such as in women with advanced ovarian cancer (see Fig. 35-8). Disadvantages include radiation exposure, artifacts created by metallic clips or prosthetic joints, and complications related to iodinated intravenous contrast material (Soper, 2001).

POSITRON EMISSION TOMOGRAPHY IMAGING

This technique is based on the use of short-lived radiotracers. Positron emission tomography (PET) has become a vital clinical tool, particularly for cancer diagnosis and management. It takes advantage of the ability of various radiochemical compounds to serve as tracers for measuring specific metabolic processes suggestive of malignancy or infection (Juweid, 2006). This enables detection of the early biochemical anomalies of cancer that precede the structural changes displayed by other imaging techniques.

The most common PET radiochemical tracer used in clinical practice is 2-[18F]-fluoro-2-deoxy-D glucose (FDG). This tracer is used to localize areas of accelerated rates of glycolysis commonly found in neoplastic cells (Goh, 2003).

The FDG-PET scan is currently being evaluated for initial imaging in women with cervical cancer (Rose, 1999). In some cases, PET scanning detects unsuspected nodal or distant metastases in women with cervical cancer more often than CT imaging. In addition, FDG-PET scanning is also being used in the surveillance of patients with ovarian cancer and has been shown to roughly correlate with findings at second-look surgery in patients who are in clinical remission (Fig. 2-23) (SchrÃ¶der, 1999).

FIGURE 2-23

A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Positron emission tomography (PET) (**A**) and PET-CT fusion (**B**) images of a woman with recurrence of ovarian cancer. **Arrows** demarcate abnormal uptake in the pelvis of FDG that represented a 1-cm lymph node. The biopsy of this lymph node revealed recurrent ovarian cancer. *(Courtesy of Dr. Dana Matthews.)*

MAGNETIC RESONANCE IMAGING

With this technology, images are constructed based on the radiofrequency signal emitted by hydrogen nuclei after they have been "excited" by radiofrequency pulses in the presence of a strong magnetic field. The radiofrequency signal emitted has characteristics called *relaxation times* . These include the T1-relaxation time (longitudinal) and the T2-relaxation time (transverse).

In a magnetic field, protons will align themselves in the same direction as the field running through the bore of the magnet. If a radiofrequency pulse is applied, these protons are forced out of alignment and rotate in phase with one another. The T1-relaxation is the time it takes for protons to realign with the magnetic field after a radiofrequency pulse is applied. T2-relaxation is the time it takes for the protons to diphase from each other after a radiofrequency pulse is applied.

Because these properties vary among tissues, they are the factors principally responsible for contrast among tissues. The signal intensity of one tissue compared with another, or contrast, can be manipulated by varying the elapsed time between applications of radiofrequency pulses, which is called *repetition time* . Further manipulation of the time between a radiofrequency pulse and sampling the emitted signal is called the *echo delay time* . Sequences with a short repetition time and short echo delay time are called *T1-weighted* and sequences with a long repetition time and long echo delay time are regarded as *T2-weighted* . As examples, the hydrogen molecules in a water-containing area, such as urine in the bladder, have longer relaxation times than those in a solid tissue such as liver. On T1-weighted images, urine in the bladder will appear dark or low signal intensity. On T2-weighted images the same urine will appear bright or high-signal intensity. The strength of the magnetic field within the bore of the magnet is

measured in tesla (T) (1 tesla = 10,000 gauss).

Technique

Standard imaging technique includes both T1- and T2-weighted sequences, acquired in two planes, usually axial and sagittal. The T1-weighted sequence most clearly delineates organ boundaries with surrounding fat, allows optimal visualization of lymph nodes, and is necessary for tissue and fluid characterization such as hemorrhagic or fat-containing lesions (Nurenberg, 1995). The T2-weighted sequence provides detailed definition of internal organ architecture, such as the zonal anatomy of the uterus and vagina, and aids identification of normal ovaries. T2-weighted images are usually superior in depicting pathologic conditions of the uterus and ovaries.

Some MR images have better resolution when a paramagnetic contrast agent such as gadolinium-DTPA is given. For example, it is routinely used for evaluation of endometrial and ovarian carcinoma. Magnetic resonance contrast agents change the local magnetic field in tissues under study. Normal and abnormal tissues react differently to the contrast, and these differences can be displayed. Concentrations and dosages of MR contrast agents are significantly lower than those used in CT imaging. Side effects are rare, and they can be used even if there is a history of allergy to other contrast agents. They undergo renal excretion within 24 hours and are extremely safe for patients with compromised renal function. During pregnancy, however, paramagnetic contrast agents should be given only if the potential benefits outweigh the potential fetal risk demonstrated in animal studies (American College of Obstetricians and Gynecologists, 2004). Gadolinium-DTPA is the only contrast material approved for MR imaging in the United States.

The multiplanar capability of MR imaging allows a study to be individualized to a specific clinical question. The transverse plane of imaging is routinely acquired in all cases, with additional sequences obtained in either the sagittal or coronal plane. The sagittal plane optimizes visualization of the uterus, whereas the coronal plane is preferred for evaluation of the ovaries.

Safety

There have been three major areas examined concerning the potential effect of MR imaging at field strengths used clinically, that is, those less than 2 tesla. These areas include the effects from static magnetic fields and gradient magnetic fields. To date, there are no reported harmful effects from MR imaging, including any mutagenic effects (American College of Radiology, 1998; International Commission on Non-ionizing Radiation Protection, 2003; Wagner, 1997).

Some, but not all, devices preclude MR imaging. For example, women with intrauterine devices can be safely imaged. Contraindications, however, include mechanically, electrically, or magnetically activated implants or devices such as internal cardiac pacemakers, neurostimulators, implantable cardiac defibrillators, implantable electronic infusion pumps, and cochlear implants. Certain intracranial aneurysm clips and any metallic foreign body in the globe of the eye contraindicate scanning (Cunningham, 2005a).

Use in Gynecology

Although sonography is preferred for initial evaluation of suspected gynecologic disease, in some cases, more detail is needed. Multiplanar imaging, superior soft tissue contrast, and large field of view offer distinct advantages of MR imaging to assess gynecologic abnormalities (Leung, 2000). For example, a major use of MR imaging is staging pelvic malignancies. Additionally, MR imaging is preferable for surveillance in women with cancer because it does not employ ionizing radiation.

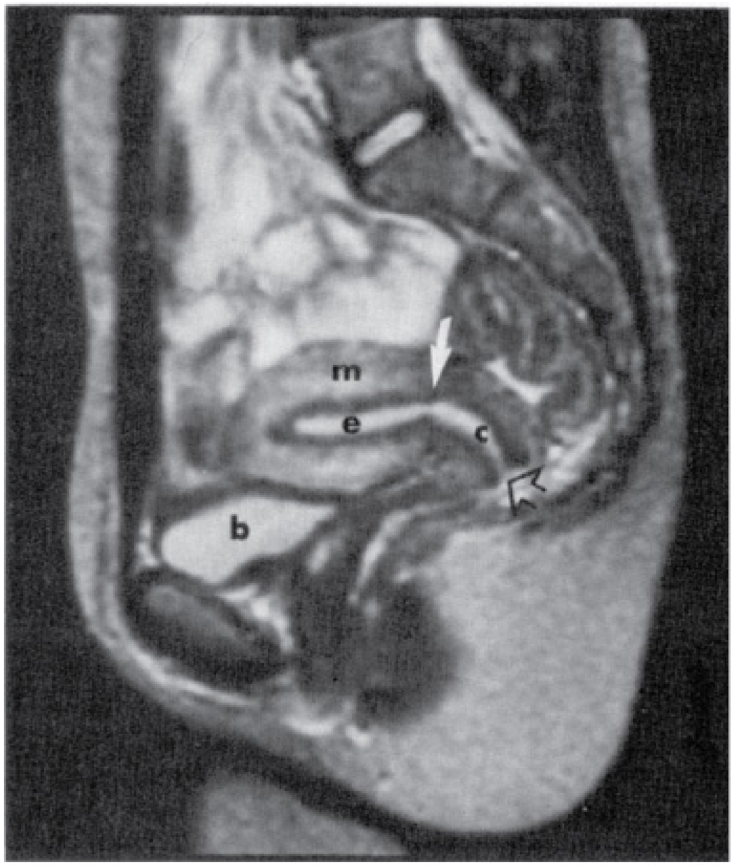
MR imaging is often used when sonographic findings are equivocal. Common indications include distorted pelvic anatomy, large masses that may be difficult to delineate with sonography, suspected adenomyosis, and some endometrial disorders (Javitt, 2005).

Normal Findings

The pelvic organs are generally moderate to low signal intensity on T1-weighted images. T2-weighted images of the menstruating uterus (Fig. 2-24) depict a high signal intensity endometrium, contiguous low signal intensity inner myometrium which is the junctional zone, and a moderate signal intensity outer myometrium (McCarthy, 1986). The cervix can be distinguished from the body of the uterus by its prominent fibrous stroma which has an overall lower signal intensity. The internal architecture of the cervix is seen on T2-weighted images as central high signal intensity (endocervical glands and mucus) surrounded by low signal

intensity (fibrous stroma) and peripheral moderate signal intensity (smooth muscle intermixed with fibrous stroma) (Lee, 1985). T2-weighted images of the vagina depict central high-signal mucosa and mucus that is surrounded by a low signal intensity muscular wall (Hricak, 1988a). Ovaries are normally seen on the T2-weighted sequence as moderately high signal intensity stroma containing very high signal intensity follicles (Dooms, 1986). The fallopian tubes are not typically visualized. Hormonal status influences the MR appearance of all structures and reflects associated physiologic changes.

FIGURE 2-24



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Sagittal T2-weighted MR image of a normal uterus and cervix. The zonal anatomy of the uterus is depicted, consisting of the endometrium (**e**) and myometrium (**m**), separated by the dark, low signal intensity junctional zone. The cervix (**c**) extends from the level of the internal os (**white arrow**) to the external os (**open arrow**) (**b** = bladder). *(Courtesy of Dr. Diane Twickler.)*

Magnetic Resonance Imaging in Gynecology

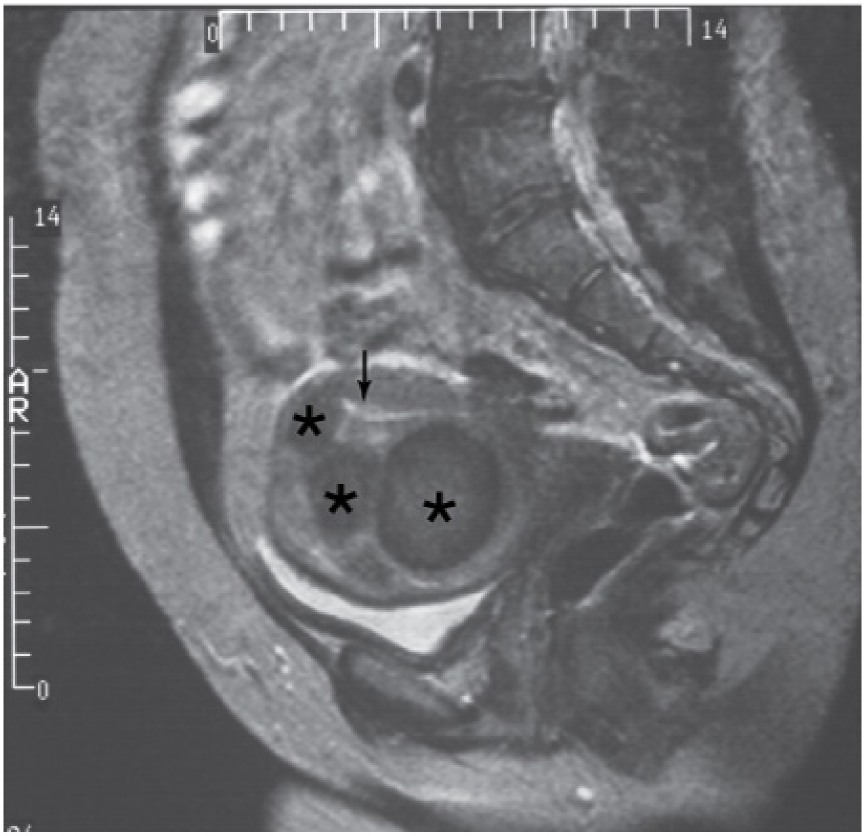
UTERUS

Leiomyomas

Magnetic resonance imaging is the most accurate tool for evaluation of leiomyomas (Ascher, 2003). Although TVS remains the initial imaging technique for evaluating women with suspected leiomyomas, there is a false-negative rate of up to 20 percent (Gross, 1983). This is due in part to its limited field of view, decreased image resolution with increasing patient body fat, and distorted anatomy because of large or multiple leiomyomas. Leiomyomas less than 2 cm are routinely not identified during TVS even when symptomatic. There are also instances in which thorough imaging is warranted, for example prior to uterine artery embolization (UAE) or hysteroscopic resection. Also, MR imaging is used when TVS is equivocal or nondiagnostic (Ascher, 2003). In addition, the effects of GnRH-agonist therapy to shrink leiomyoma volume can be quantified with MR imaging (Lubich, 1991).

As shown in Figure 2-25, leiomyomas have a specific MR appearance and thus can be differentiated from adenomyosis or adenomyoma with 90-percent accuracy (Mark, 1987; Togashi, 1989). This is important when myomectomy is considered. Leiomyomas as small as 0.5 cm are best seen on T2-weighted images and appear as round, sharply marginated, low signal intensity masses relative to the myometrium (Hricak, 1986). Multiplanar views allow for accurate localization as subserosal, intramural, or submucosal. The stalk of a prolapsed submucosal leiomyoma can be reliably identified with MR imaging and confirm its accessibility to hysteroscopic resection. Intramural or subserosal leiomyomas are frequently circumscribed by a high signal intensity rim which represents edema from dilated lymphatics and veins. Tumors larger than 3 cm often are heterogeneous because of varying degrees and types of degeneration (Hricak, 1986; Yamashita, 1993).

FIGURE 2-25



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Sagittal T2-weighted MR image of a uterus demonstrating four leiomyomas. The leiomyomas (*****) appear as round, sharply marginated, dark, low-signal-intensity masses in the posterior myometrium. The endometrium is identified as the bright, high-signal-intensity line anterior to the leiomyomas (**arrow**). *(Courtesy of Dr. Diane Twickler.)*

Enhancement of leiomyomas with intravenous gadolinium contrast may be predictive of successful response to uterine artery embolism. Hypervascularity, which is seen as a bright signal on T2-weighted images after intravenous gadolinium, correlates with a good response to UAE (Jha, 2000). In contrast, leiomyomas with negligible enhancement and high signal intensity on T1-weighted sequences do not respond to UAE. Contrast MR imaging is also useful for monitoring tumor response after UAE. Successfully embolized leiomyomas demonstrate a decrease in size and no enhancement with contrast, consistent with degeneration (DeSousa, 1999).

Magnetic resonance imaging guidance of focused ultrasound therapy (MR imaging-FUS) has been used to treat symptomatic leiomyomas (Cline, 1992). Without MR guidance, focused ultrasound therapy is hampered by difficulty in precise targeting of the

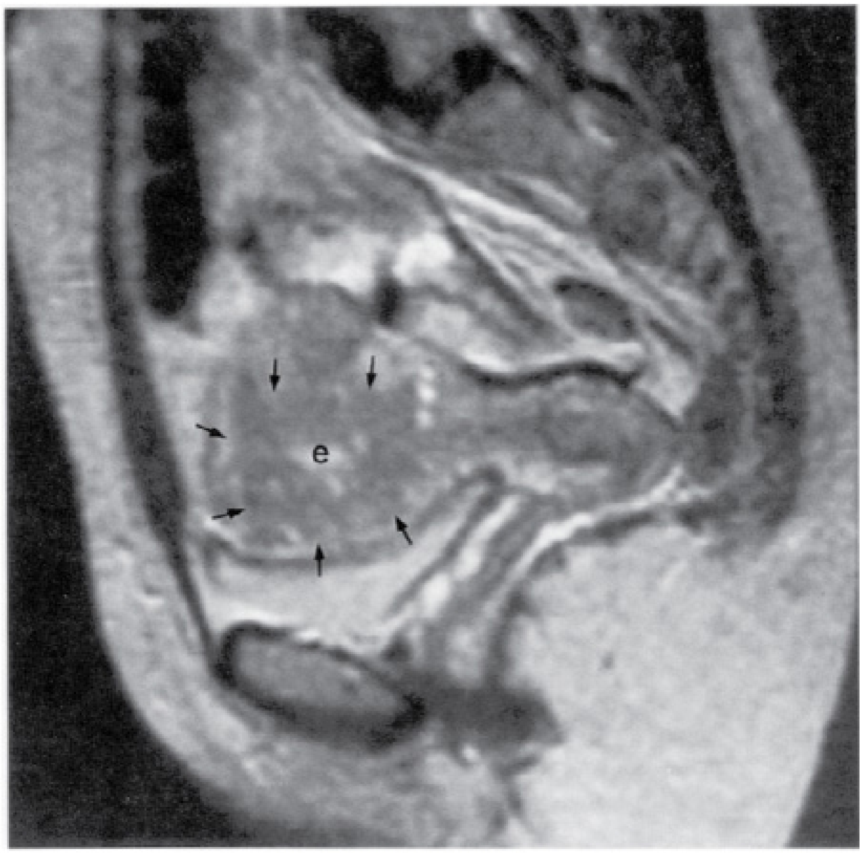
beam and in receiving feedback regarding thermal damage created. Fortunately, excellent soft-tissue resolution with MR imaging enables accurate tissue targeting. Moreover, magnetic resonance imaging parameters have an intrinsic sensitivity to temperature. Thus, MR imaging can measure accurate, near real-time thermometry, and thermal damage created by focused ultrasound can be assessed immediately (Hindley, 2004). A series of high-power ultrasound pulsesâ€"sonicationsâ€"are directed into the leiomyoma, and power is adjusted until an adequate temperature and thermal dose is reached. Pulse duration is generally about 15 seconds, and the interval between pulses, 3 minutes, allows tissues to cool between treatments. The average procedure duration is about 3.5 hours (Hindley, 2004).

Preliminary studies indicate that MR imaging-FUS therapy is a safe and feasible minimally invasive alternative for leiomyoma treatment (Chen, 2005; Stewart, 2003). It may provide short-term symptom relief with the advantage of a quicker recovery and few major adverse events. However, little information is available on costs and long-term results compared with other treatments such as UAE and surgery.

Adenomyosis

To diagnose adenomyosis, MR imaging has been shown to be equivalent or superior to sonography, with a sensitivity of 88 to 93 percent and a specificity of 66 to 91 percent (Ascher, 1994; Reinhold, 1996). Its contrast to the sharply demarcated, homogeneous MR-imaging appearance of leiomyomas is shown in Figure 2-26. Areas of adenomyosis contain internal punctate foci of increased signal on both T1- and T2-weighted images, and they are oval-shaped with ill-defined margins (Togashi, 1988, 1989). The highly signal intense foci represent ectopic endometrium and cystically dilated endometrial glands, with or without hemorrhage (Reinhold, 1996). Diffuse areas of adenomyosis will be evident by thickening greater than 11 mm of the low signal intensity junctional zone, that is, the inner myometrium, and linear high signal intensity striations radiating out from the endometrial surface. These striations are thought to represent direct invasion of the endometrial zona basalis into the underlying myometrium. Contrast administration does not increase the diagnostic accuracy for adenomyosis (Outwater, 1998).

FIGURE 2-26



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Sagittal T2-weighted MR image of a uterus with diffuse adenomyosis. Adenomyosis is shown as circumferential thickening of the junctional zone (**arrows**) (**e** = endometrium). *(Courtesy of Dr. Diane Twickler.)*

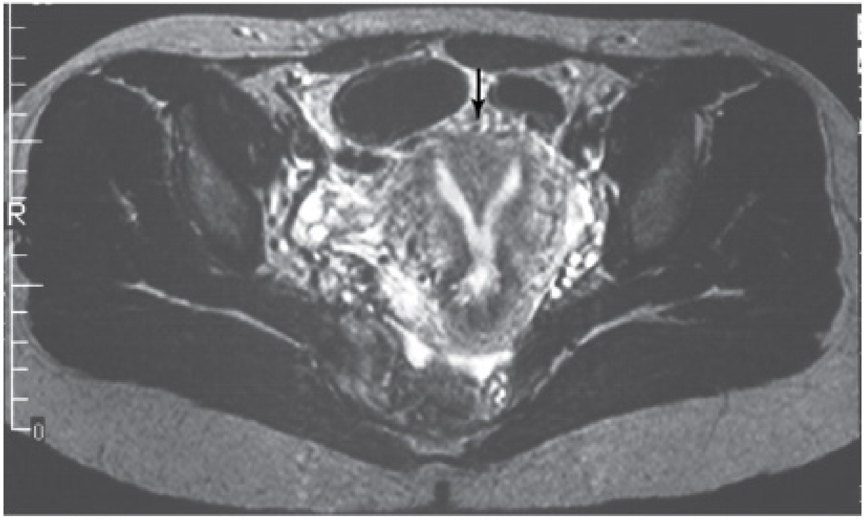
Congenital Anomalies

MÃ¼llerian duct anomalies comprise a spectrum of developmental malformations associated with varying degrees of adverse reproductive outcomes. They are traditionally diagnosed using sonography and hysterosalpingography with or without saline infusion. Until recently, further evaluation required laparoscopy, laparotomy, or hysteroscopy. These invasive techniques have now largely been replaced by MR imaging (Troiano, 2003). It is the preferred procedure for evaluating mÃ¼llerian duct anomalies and has an accuracy of up to 100 percent (Carrington, 1990; Doyle, 1992; Fedele, 1989; Fielding, 1996; Pellerito, 1992a).

One example of MR imaging superiority is differentiation of septate and bicornuate uteri, which is imperative with regard to their clinical implications and surgical treatment. In a bicornuate uterus, the dividing septum is composed of myometrium, and with MR imaging it is characterized by signal intensity of myometrium. The endometrium of a bicornuate uterus has a normal width and lines two uterine cavities that communicate, as demonstrated by their confluent increased signal intensity (Carrington, 1990; Fedele, 1989; Pellerito, 1992a). The contour of the fundus is concave. Finally, the bicornuate uterus typically has a significant notchâ€"larger than 1 cmâ€"in the fundus between the two horns, and the intercornual diameter is greater than 4 cm (Carrington, 1990; Fedele, 1989; Pellerito, 1992a).

The septate uterus is a result of incomplete resorption of the final fibrous septum between the two uterine horns. It is composed of collagen which has low signal intensity on both T1- and T2-weighted images (Fig. 2-27). The fundal contour of the septate uterus can be convex, flattened, or mildly concave, but the fundal indentationâ€"the notchâ€"is less than 1 cm (Leung, 2000). Also in contrast to the bicornuate uterus, the intercornual diameter of the septate uterus is not increased, and thus each uterine cavity is smaller than usual (Carrington, 1990; Forstner, 1994).

FIGURE 2-27

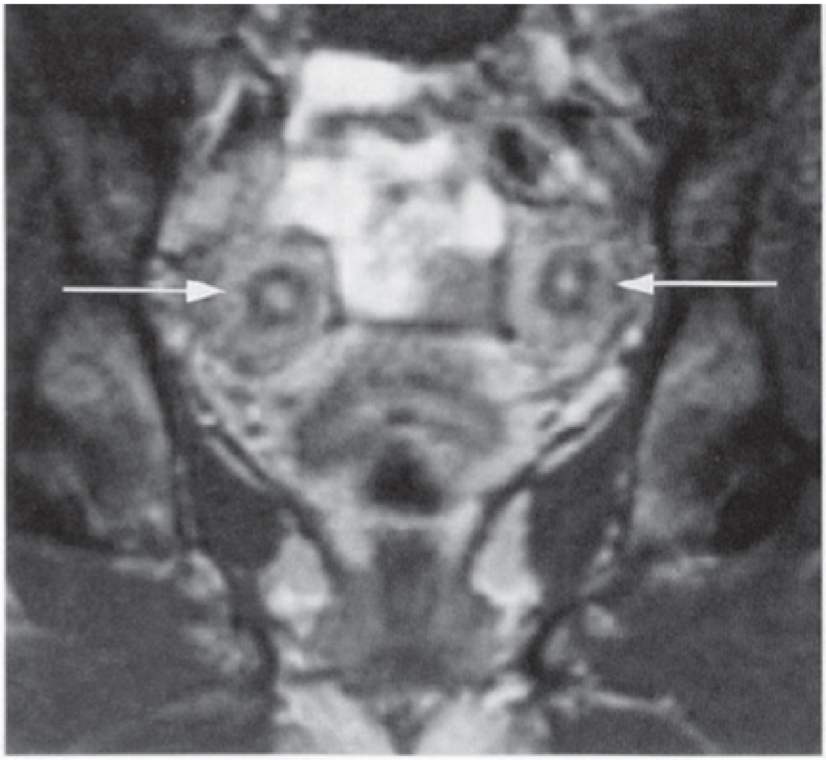


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Transaxial T2-weighted MR image of a septate uterus. A low-signal-intensity fibrous septum separates the two high-signal-intensity endometrial cavities (**arrow**) and the fundal contour is normal, without indentation. *(Courtesy of Dr. Diane Twickler.)*

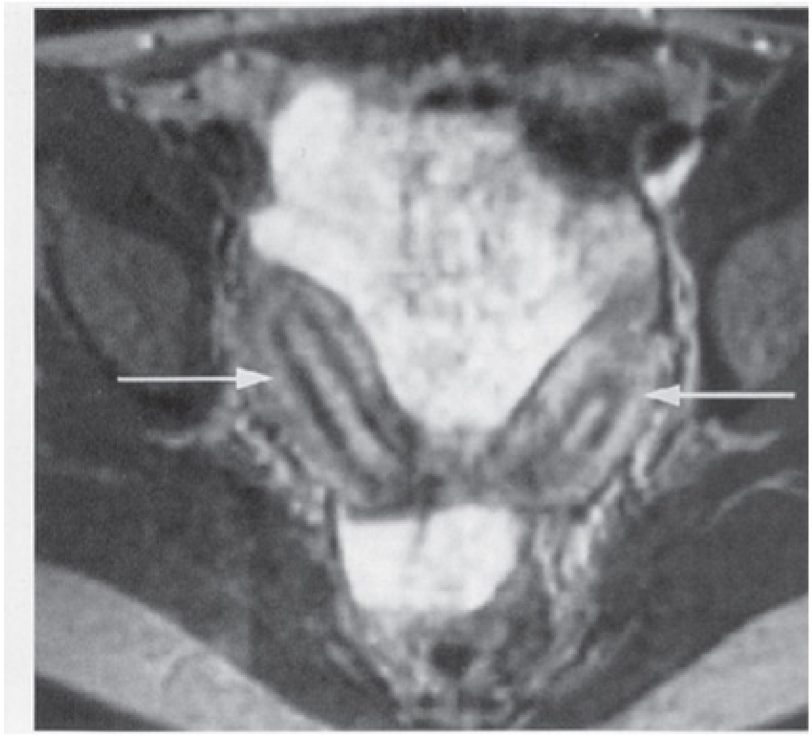
Other anomalies for which MR imaging is used include uterine didelphys and unicornuate uterus with its rudimentary horn (Fig. 2-28). It can also determine whether endometrium is contained within the rudimentary horn and whether the horn communicates with the main uterine cavity, a finding of considerable clinical importance (see Chap. 18, Unicornuate Uterus) (Leung, 2000). The superior resolution of MR imaging is also important for planning surgical treatment of cloacal anomalies (Nurenberg, 1995; Pena, 1990).

FIGURE 2-28



A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Uterine didelphys. **A.** Coronal T2-weighted MR image demonstrates two distinct and widely separate endometrial cavities (**arrows**). **B.** Transaxial T2-weighted MR image shows two distinct uterine horns (**arrows**). *(Courtesy of Dr. Diane Twickler.)*

ADNEXAL MASSES

Sonography is the imaging modality of choice for initial evaluation of adnexal masses, whereas MR imaging is useful in some cases in which sonography is inconclusive. Magnetic resonance imaging frequently can further characterize lesions, for example differentiate adnexal from uterine masses. It has higher accuracy to diagnose specific adnexal lesions compared with sonography: 60 to 95 percent versus 53 to 88 percent (Leung, 2000; Smith, 1988; Stevens, 1991; Thurnher, 1990).

GYNECOLOGIC MALIGNANCY

Cervical Cancer

Although not used for screening, MR imaging is excellent for preoperative staging of gynecologic neoplasms. Its superior soft-tissue contrast resolution and ability to image directly in multiple planes allows evaluation of lymphadenopathy and local tumor extension.

Although CT imaging remains the standard of care for the assessment of nodal disease and distant metastases, MR imaging consistently outperforms clinical and CT staging for cervical cancer in the assessment of local tumor extension. Studies of preoperative MR imaging evaluation have shown it to be both cost-effective and therapeutically valuable (Durfee, 2000; Hricak, 1996). Current recommendations for MR imaging with cervical cancer include tumor with a transverse diameter >2 cm by physical examination, endocervical or predominately infiltrative tumors that cannot be accurately assessed clinically, and women who are pregnant or have concomitant uterine lesions, such as leiomyomas, that make assessment difficult (Ascher, 2001). When parametrial and sidewall invasion are difficult to assess clinically, MR imaging may play an important role in their evaluation

(Ascher, 2001). It has a 95-percent negative-predictive value for parametrial invasion, allowing the absence of parametrial invasion to be determined with confidence (Hricak, 1988b; Lien, 1991; Subak, 1995).

Endometrial Cancer

Surgery is currently the most accurate staging method. For the same advantages cited for cervical cancer, MR imaging has recently been gaining acceptance to evaluate endometrial carcinoma (Ascher, 2001). Knowledge of the degree of myometrial and cervical extension affects the type of hysterectomy selected, lymph node dissection, and decision to use preoperative intracavitary radiation (Boronow, 1984; Frei, 2000; Larson, 1996). Therefore, MR imaging is recommended if there is a high probability for lymph node metastases, that is, high-grade tumor, papillary or clear cell histology, or cervical invasion, or if there is a need for multifactorial assessment of myometrial, cervical, and lymph node involvement (Ascher, 2001).

Ovarian Cancer

Magnetic resonance imaging for ovarian neoplasms is reserved for evaluation when transvaginal sonography is indeterminate or nondiagnostic (Nurenberg, 1995). Magnetic resonance imaging is particularly useful to assess the origin of an adnexal massâ€"uterine, ovarian, or nongynecologicâ€"and if ovarian in origin, determining whether the mass is neoplastic versus non-neoplastic and malignant versus benign (Ascher, 2001).

Sensitivity of MR imaging for detecting adnexal pathology ranges from 87 to 100 percent and is therefore similar to that of sonography and CT (Siegelman, 1999). The accuracy of MR imaging ranges from 83 to 95 percent to characterize an ovarian mass as benign or malignant, compared with 53 to 88 percent with sonography and 66 to 94 percent for CT (Komatsu, 1996; Stevens, 1991; Yamashita, 1995). In a large prospective trial to evaluate ovarian masses detected with transvaginal sonography, MR imaging was more accurate than CT or Doppler sonography for diagnosing malignancy (Kurtz, 1999). It is also more accurate than CT for detecting extrapelvic peritoneal metastases and identifying omentum, bowel, and osseous and vascular structures (Low, 1995). Finally it can be used to evaluate non-resectability (Forstner, 1995).

MR evaluation of an adnexal mass should include gadolinium-enhanced images to assess tumor vascularity and fat- saturation techniques to differentiate blood from fat on T1-weighted high signal intensity lesions (Ascher, 2001). Although histology cannot be diagnosed, findings that are suspicious for malignancy include enhancing solid components, thick septations, nodules, and papillary projections.

UROGYNECOLOGY

Very fast-sequence MR imaging, termed *dynamic imaging* , allows detailed delineation of pelvic structures in women with stress urinary incontinence or prolapse of the bladder, uterus, or rectum. Grading systems of pelvic organ prolapse and pelvic floor relaxation based on dynamic imaging have been developed by Barbaric and colleagues (2001). Other imaging techniques have also been developed for evaluation of prolapse (Fielding, 1998). These include placement of various contrast materials, for example, lubricating gel or sonographic transmission gel, into the vagina and rectum to assess vaginal vault prolapse and rectocele, as well as a suitable replacement for defecography to evaluate prolapse (see Chap. 25, Evacuation Proctography). (Kelvin, 2000; Lienemann, 1997; Schoenenberger, 1998). Most recently, MR imaging with 3-D reconstruction has been used to describe levator muscle morphometry in term pregnant nulliparous women to evaluate the effect of pregnancy on the pelvic floor (Boreham, 2005).

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NORMAL VAGINAL FLORA

Vaginal flora of a normal asymptomatic reproductive-aged woman includes multiple aerobic or facultative species as well as obligate anaerobic species (Table 3-1). Of these, anaerobes are predominant and outnumber aerobic species approximately 10 to 1 (Bartlett, 1977).

Table 3-1 Lower Reproductive Tract Bacterial Flora
Species or Group of Organism
Aerobes
Gram-positive
Lactobacillus spp
Diphtheroids
Staphylococcus aureus
Staphylococcus epidermidis
Group B Streptococcus
Enterococcus faecalis
Staphylococcus spp
Gram-negative
Escherichia coli
Klebsiella spp
Proteus spp
Enterobacter spp
Acinetobacter spp
Citrobacter spp
Pseudomonas spp
Anaerobes

Gram-positive cocci
Peptostreptococcus spp
Clostridium spp
Gram-positive bacilli
Lactobacillus spp
Propionibacterium spp
Eubacterium spp
Bifidobacterium spp
Gram-negative
Prevotella spp
Bacteroides spp
Bacteroides fragilis group
Fusobacterium spp
Veillonella spp
Yeast
Candida albicans and other spp

One study of 55 asymptomatic reproductive-aged women found a mean of 4.2 and 2.1 bacterial species recovered from the endocervix and the endometrial cavity, respectively (Hemsell, 1989). Of the species recovered, 17 percent were recovered from the endometrium only, 50 percent were recovered from the endocervix only, and the remainder was recovered from both sites. This implies that there is access to the upper reproductive tract by certain bacterial species normally found in vaginal flora.

The function of and reason for bacterial colonization of the vagina remains unknown. Bacteria do exist in a symbiotic relationship with the host and are alterable, depending on the microenvironment. These organisms localize where their survival needs are met, and have exemption from the infection-preventing destructive capacity of the host.

Within this vaginal ecosystem, some microorganisms produce substances such as lactic acid and hydrogen peroxide that inhibit nonindigenous organisms (Marrazzo, 2006). In addition, several other antibacterial compounds, termed *bacteriocins,* provide a similar role and include peptides such as acidocin and lactacin. Moreover, some species have the ability to produce proteinaceous adhesions and attach to vaginal epithelial cells.

For protection from many of these toxic substances, the vagina secretes leukocyte protease inhibitor. This protein protects local tissues against toxic inflammatory products and infection.

Vaginal pH

Typically, the vaginal pH ranges between 4 and 4.5. Although not completely understood, it is believed to result from *Lactobacillus* species' production of lactic acid, fatty acids, and other organic acids. In addition, amino acid fermentation by anaerobic bacteria results in organic acid production as does bacterial protein catabolism. Glycogen present in healthy vaginal mucosa is believed to

provide nutrients for many species in the vaginal ecosystem. Accordingly, as glycogen content within vaginal epithelial cells diminishes after menopause, this decreased substrate for acid production leads to a rise in vaginal pH (Chap. 21, Lower Reproductive Tract Changes). Specifically, Caillouette and associates (1997) showed that a vaginal pH of 6.0 to 7.5 was strongly suggestive of menopause in the absence of symptoms. Moreover, serum follicle-stimulating hormone (FSH) levels and vaginal pH were positively correlated, whereas an inverse relationship was noted between those two and serum estradiol levels.

Altered Flora

Changing any element of this ecology may alter the prevalence of various species. For example, postmenopausal women not receiving estrogen replacement and young girls have a lower prevalence of *Lactobacillus* species compared with reproductive-aged women. Devillard and colleagues (2004) reported that hormone replacement therapy restored vaginal lactobacilli populations, which protected against reproductive tract pathogens.

The menstrual cycle may also alter normal flora. Transient changes are observed, predominantly during the first part of the menstrual cycle, and are presumed to be associated with hormonal changes (Keane, 1997).

Several other events predictably alter lower reproductive tract flora and may lead to patient infection. Treatment with a broad-spectrum antibiotic or menstruation may result in symptoms attributed to inflammation from *Candida albicans* or other *Candida* species. Menstrual fluid also may serve as a source of nutrients for several bacterial species, resulting in their overgrowth. What role this plays in the development of upper reproductive tract infection following menstruation is unclear, but an association may be present.

Hysterectomy with removal of the cervix changes lower reproductive tract flora, with or without prophylactic antimicrobial administration. Usually, more anaerobic species are recovered from the vagina postoperatively, with a particular increase in the prevalence of *Bacteroides fragilis.* Increased prevalence is also observed for *Escherichia coli* and *Enterococcus* species. These three species are frequently observed in cultures obtained from women who develop pelvic infections following hysterectomy, but similar increases are also seen in vaginal cultures obtained after hysterectomy in asymptomatic patients (Hemsell, 1988; Ohm, 1975).

Bacterial Vaginosis (BV)

This common and complex clinical syndrome reflects abnormal vaginal flora, and is poorly understood. It has been variously named, and former terms include *Haemophilus* vaginitis, *Corynebacterium* vaginitis, *Gardnerella* or anaerobic vaginitis, and nonspecific vaginitis.

For unknown reasons, the vaginal flora's symbiotic relationship shifts to one in which there is overgrowth of anaerobic species including *Gardnerella vaginalis, Ureaplasma urealyticum, Mobiluncus* species, *Mycoplasma hominis,* and *Prevotella* species. Bacterial vaginosis (BV) is also associated with a significant reduction or absence of the normal hydrogen peroxide-producing *Lactobacillus* species. Whether an altered ecosystem leads to lactobacilli disappearance or whether its disappearance results in the changes observed with BV is unknown.

RISK FACTORS

This condition is not considered by the Centers for Disease Control and Prevention (CDC) consensus group to be a sexually transmitted disease (STD), and it is seen in women without previous sexual experience. Many risk factors, however, are associated with sexual activity, and an increased risk of acquiring STDs has been reported in affected women (Table 3-2). Moreover, a possible role of sexual transmission in the pathogenesis of recurrent BV has been proposed by Bradshaw and colleagues (2006). Successful prevention of BV is limited, but elimination or diminished use of vaginal douches may be beneficial.

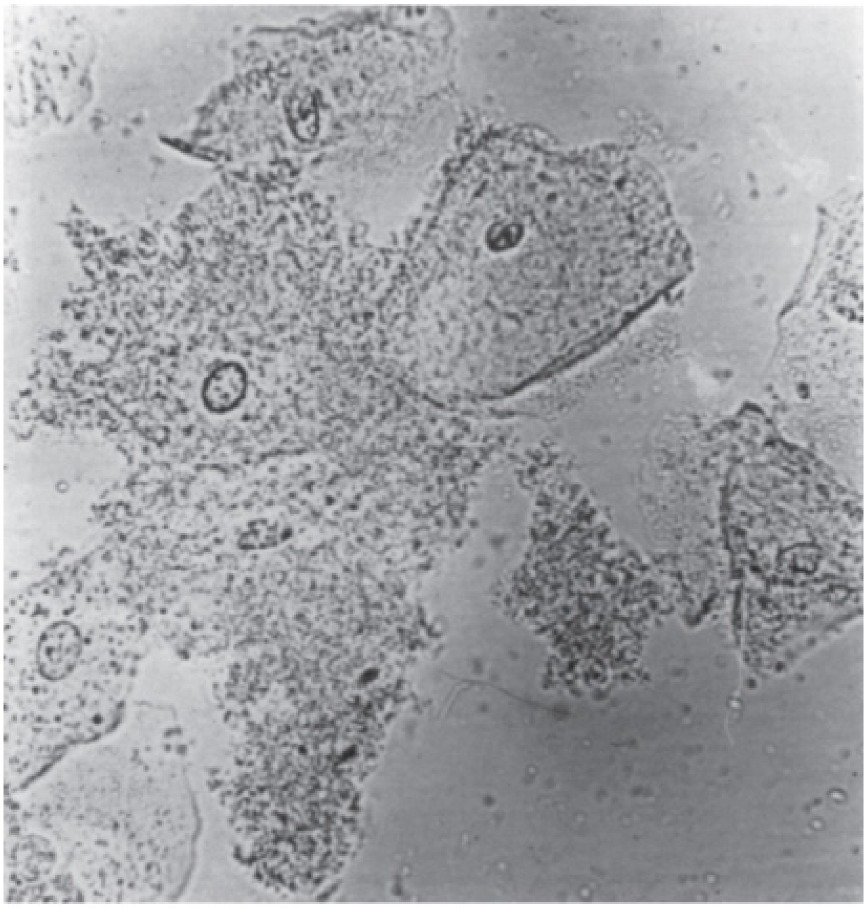
Table 3-2 Bacterial Vaginosis Risk Factors
Oral sex
Douching
Black race
Cigarette smoking
Sex during menses
Intrauterine device
Early age of sexual intercourse
New or multiple sexual partners
Sexual activity with other women

DIAGNOSIS

Bacterial vaginosis is reported by some to be the most frequent cause of vaginal symptoms resulting in health care visits. Of symptoms, a nonirritating, malodorous vaginal discharge is characteristic, but may not always be present. The vagina is usually not erythematous, and cervical examination reveals no abnormalities.

Clinical diagnostic criteria were first proposed by Amsel and associates (1983) and include: (1) microscopic evaluation of a saline "wet prep" of vaginal secretions, (2) determination of the vaginal pH, and (3) release of volatile amines produced by anaerobic metabolism. Clue cells are the most reliable indicators of BV and were originally described by Gardner and Dukes (1955) (Fig. 3-1). These vaginal epithelial cells contain many attached bacteria, which create a poorly defined stippled cellular border. The positive predictive value of this test for the presence of BV is 95 percent.

FIGURE 3-1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photograph of saline wet preparation reveals clue cells. Squamous cells are covered with bacteria to the extent that cell borders are blurred and nuclei are not visible. A saline preparation, also termed a *wet prep,* is made by mixing a sample of vaginal discharge obtained with a cotton swab and a few drops of saline on a microscope slide. *(From Kuhn, 2004, with permission.)*

Adding 10 percent potassium hydroxide (KOH) to a fresh sample of vaginal secretions releases volatile amines that have a fishy odor. This is often colloquially referred to as a *whiff test.* The odor is frequently evident even without KOH. Similarly, alkalinity of seminal fluid and blood are responsible for odor complaints after intercourse and with menses. The finding of both clue cells and a positive whiff test is pathognomonic, even in asymptomatic patients.

Characteristically with BV, the vaginal pH is >4.5 and results from diminished acid production by bacteria. Similarly, *Trichomonas vaginalis* infection is also associated with anaerobic overgrowth and resultant elaborated amines. Thus, women diagnosed with BV should have no microscopic evidence of trichomoniasis.

Several gynecologic adverse health outcomes have been observed in women with BV, including vaginitis, endometritis, postabortal endometritis, pelvic inflammatory disease unassociated with *Neisseria gonorrhoeae* or *Chlamydia trachomatis,* and acute pelvic infections following pelvic surgery, especially hysterectomy.

TREATMENT

Three regimens have been proposed by the 2006 Centers for Disease Control and Prevention BV working group and are for nonpregnant women (Table 3-3). Cure rates with these regimens range from 80 to 90 percent at 1 week, but within 3 months, 30 percent of women have experienced a recurrence of altered flora. At least half have another episode of symptoms associated with this flora change, many of which are correlated with heterosexual contacts (Amsel, 1983; Gardner, 1955; Wilson, 2004). However,

treatment of male sexual partners does not benefit women with this recurring condition and is not recommended. Moreover, other forms of therapy such as introduction of lactobacilli, acidifying gel, and use of probiotics have shown inconsistent effectiveness.

Table 3-3 Recommended Treatment of Bacterial Vaginosis

Agent	Dosage
Metronidazole	500 mg orally twice daily for 7 days
Metronidazole gel 0.75%	5 g (1 full applicator) intravaginally once daily for 5 days
Clindamycin cream 2%	5 g (1 full applicator) intravaginally at bedtime for 5 days

From Centers for Disease Control and Prevention, 2006, with permission.

ANTIBIOTICS

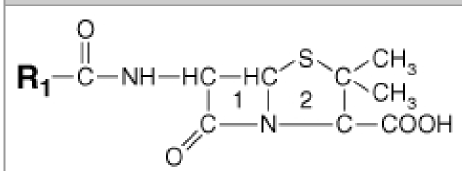
Antibiotics are commonly used in gynecology to restore altered flora or treat various infections. The ideal antibiotic is one that exhibits almost complete bioavailability from either oral or parenteral administration, acts promptly to eradicate a diverse variety of aerobic and anaerobic bacteria, fails to induce bacterial resistance, and is nontoxic, nonsensitizing, inexpensive, and easily produced. It does not exist. Despite this, there are many effective antibiotics available for the treatment of gynecologic infection.

Penicillins

STRUCTURE

The heart of all penicillins is a thiazolidine ring with an attached β-lactam ring and a side chain (Fig. 3-2). The β-lactam nucleus provides antibacterial activity, which is primarily against gram-positive aerobic bacteria. Because of the numerous substitutions at R_1 , a variety of antibiotics with altered antibacterial spectra and pharmacologic properties have been synthesized (Table 3-4). In addition, clavulanic acid and sulbactam β-lactamase inhibitors have been combined with one of several existing penicillins. This enhances the spectrum of activity against a broader variety of aerobic and anaerobic bacteria, whose primary defense mechanism is production of an enzyme (β-lactamase) that opens the β-lactam ring, inactivating the antibiotic.

FIGURE 3-2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Basic chemical structure of penicillins.

Table 3-4 Penicillin Family Classification
Type and Administration Route
Natural
Penicillin G (oral, IV, IM)
Penicillin V phenoxyethyl (oral)
Penicillinase-resistant
Cloxacillin (oral)
Dicloxacillin (oral)
Methicillin (IV, IM)
Nafcillin (IV, IM)
Oxacillin (oral, IV, IM)
Aminopenicillins
Amoxicillin (oral)
Ampicillin (oral, IV, IM)
Bacampicillin (oral)
Carboxycillins (IV, IM)
Azlocillin
Carbenicillin
Ticarcillin
Ureidopenicillins (IV, IM)
Mezlocillin
Piperacillin
Penicillin plus β-lactamase inhibitor
Amoxicillin-clavulanic acid (oral, IV, IM)
Ampicillin-sulbactam (IV, IM)
Ticarcillin-clavulanic acid (IV, IM)

IM = intramuscular; IV = intravenous.

ADVERSE REACTIONS

Table 3-5 lists adverse reactions to penicillins (Mayo Clinic, 1991). Up to 10 percent of the general population may manifest an allergic reaction to penicillins. The lowest risk is associated with oral preparations, whereas the highest follows those combined with procaine and given intramuscularly. True anaphylactic reactions are rare, and mortality ranges between 1 in every 50,000 to 60,000 treatment regimens. If penicillin allergy is noted, yet treatment is still required, desensitization can be performed as described by Wendel and co-workers (1985) and outlined at the CDC website: http://www.cdc.gov/std/treatment/2006/penicillin-allergy.htm .

Table 3-5 Penicillin Adverse Reactions

Adverse Reaction	**Representative Penicillin**
Allergic	
Anaphylaxis	Any penicillin
Urticaria	Any penicillin
Drug fever	Any penicillin
Serum sickness	Penicillin G
Delayed hypersensitivity	Ampicillin
Exfoliative dermatitis	Any penicillin
Neurologic	
Seizure	Penicillin G
Dizziness, paresthesias	Penicillin G procaine
Neuromuscular irritability	Penicillin G
Hematologic	
Hemolytic anemia	Penicillin G
Neutropenia	Oxacillin, piperacillin, penicillin G
Thrombocytopenia	Piperacillin
Platelet dysfunction	Carbenicillin
Renal	
Interstitial nephritis	Methicillin, ampicillin, any penicillin
Hepatic	
Increased transaminases	Oxacillin, nafcillin, any penicillin
Gastrointestinal	
Nausea, vomiting	Ampicillin

Diarrhea	Ampicillin
Pseudomembranous colitis	Any penicillin
Electrolyte abnormalities	
Sodium overload	Carbenicillin
Hypokalemia	Carbenicillin
Thrombophlebitis	Nafcillin, oxacillin

CLINICAL APPLICATIONS

Excellent tissue penetration is achieved with these agents. Penicillin remains the primary drug for treatment of syphilis, and this family of antibiotics is also useful in treating skin infections and breast abscesses. Moreover, the ureidopenicillins and those combined with a β-lactamase enzyme inhibitor are effective against acute community-acquired or postoperative pelvic infections. The combination of amoxicillin and clavulanic acid provides the best oral broad-spectrum antibiotic coverage.

Cephalosporins

STRUCTURE

Cephalosporins also are β-lactam antimicrobials that are semisynthetically derived from a compound produced by the fungus *Cephalosporium acremonium.* Substitutions at the R_1 or R_2 sites of the cephalosporin nucleus significantly alter the spectrum of activity, potency, toxicity, and half-life of these antibiotics (Fig. 3-3). Organization of these qualities has resulted in their division into first-, second-, or third-generation cephalosporins. Although possibly a marketing tool, this classification does allow grouping based on general spectra of activity. Those commonly used by the gynecologists are presented in Table 3-6.

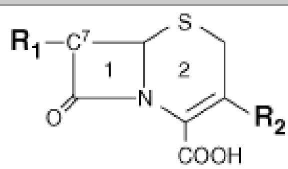
Table 3-6 Cephalosporin Classification

Generic Name and Route of Administration	
First-generation	
Cefadroxil	(oral)
Cephalexin	(oral)
Cephazolin	(IV)
Second-generation	
Cefaclor	(oral)
Cefotetan	(IV, IM)
Cefoxitin	(IV, IM)
Cefuroxime	(IV, IM)
Cefuroxime axetil	(oral, IV, IM)
Third-generation	

Cefixime	(oral)
Cefoperazone	(IV, IM)
Cefotaxime	(IV, IM)
Cefpodoxime	(oral)
Ceftazidime	(IV, IM)
Ceftizoxime	(IV, IM)
Ceftriaxone	

IM = intramuscular; IV = intravenous.

FIGURE 3-3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Chemical nuclear structure of the cephalosporins, produced by alterations in the molecular structure of the basic cephalosporin nucleus at the R_1 and R_2 positions.

ADVERSE REACTIONS

Rash and other hypersensitivity reactions are the most common, and may develop in up to 3 percent of patients. Cephalosporins are β-lactam antibiotics and, if used in those allergic to penicillin, may create the same or accentuated response. Theoretically, this may happen in up to 16 percent of patients (Saxon, 1987). Thus, if an individual developed anaphylaxis with penicillin therapy, cephalosporin administration is contraindicated.

CLINICAL APPLICATIONS

First-generation cephalosporins are used primarily for surgical prophylaxis and in the treatment of superficial skin cellulitis. Their activity spectrum is greatest against gram-positive aerobic cocci, with some activity against community-acquired gram-negative rods. However, there is little activity against β-lactamase producing organisms or anaerobic bacteria. Despite this inactivity against many pathogens of pelvic infection that may be acquired during surgery, there is prophylactic efficacy.

Second-generation cephalosporins have enhanced activity against gram-negative aerobic and anaerobic bacteria, with some diminution in effectiveness against aerobic gram-positive cocci. Their primary use is in surgical prophylaxis or for single-agent therapy of major community-acquired or postoperative pelvic infections.

Third-generation cephalosporins are effective in treatment of major postoperative pelvic infections, including abscess. However, they are used primarily in the treatment of postoperative respiratory tract infections. These agents have documented efficacy as prophylactic agents, but should be reserved for therapy.

Aminoglycosides

STRUCTURE AND CLINICAL APPLICATIONS

This family of compounds includes gentamicin, tobramycin, netilmicin, and amikacin. They differ in antimicrobial activity based on the various amino sugars that form the lateral chains of the central aminoglycoside nucleus. Of the aminoglycosides, gentamicin is primarily selected because of its low cost and clinical efficacy for pathogens recovered from pelvic infections. For gynecologists, it may be combined with clindamycin with or without ampicillin as a regimen for treatment of serious pelvic infections. Alternatively, gentamicin may be joined with ampicillin and metronidazole. Lastly, it can be used as single-agent therapy for pyelonephritis.

ADVERSE REACTIONS

Aminoglycosides have the potential for significant patient toxicity (Table 3-7). The inner ear is particularly susceptible to aminoglycosides because of selective accumulation within the hair cells and prolonged half-life within inner ear fluids. Those with vestibular toxicity complain of headaches, nausea, tinnitus, and loss of equilibrium. Cochlear toxicity results in high-frequency hearing loss. If either of these develops, aminoglycoside administration must be stopped promptly. Ototoxicity may be permanent, and risk correlates positively with dose and duration of therapy.

Table 3-7 Aminoglycoside Toxicity
Major
• Ototoxicity
Auditory
Vestibular
• Nephrotoxicity
• Neuromuscular blockade
Minor
• Skin rash
• Drug fever

Nephrotoxicity is reversible, and may develop in up to 25 percent of patients (Bertino, 1993). Risk factors include older age, renal insufficiency, hypotension, volume depletion, frequent dosing intervals, treatment for 3 or more days, multiple antibiotic administration, or multisystem disease. Toxicity leads to a nonoliguric decrease in creatinine clearance and resultant rise in serum creatinine levels.

Neuromuscular blockade is a rare but potentially life-threatening complication, and is dose-related. This family of antibiotics inhibits presynaptic acetylcholine release, blocks acetylcholine receptors, and prevents presynaptic calcium absorption. For this reason, aminoglycoside contraindications include myasthenia gravis or concurrent succinylcholine use. Blockade frequently follows rapid intravenous infusion. For this reason, aminoglycosides are ideally given intravenously over at least 30 minutes. Toxicity is usually detected before respiratory arrest, and at its first signs, intravenous calcium gluconate is administered to reverse this form of aminoglycoside toxicity.

DOSING

Multiple Doses

Aminoglycosides may be parenterally dosed every 8 hours in those with normal renal function. For critically ill patients, an initial dose of between 1.5 and 2 mg/kg for gentamicin, tobramycin, and netilmicin, and 7.5 and 15 mg/kg for amikacin is recommended. Subsequently, maintenance doses are calculated to deliver 3 to 5 mg/kg/d of ideal body weight for the first three aminoglycosides listed above and 15 mg/kg/d for amikacin.

If a patient has decreased renal function, there should be dose reduction or interval lengthening or both. The formula listed allows one to calculate a rough estimate of creatinine clearance so proper adjustments can be made. This formula is for male patients. The result, multiplied by 0.85, will give a value for female patients.

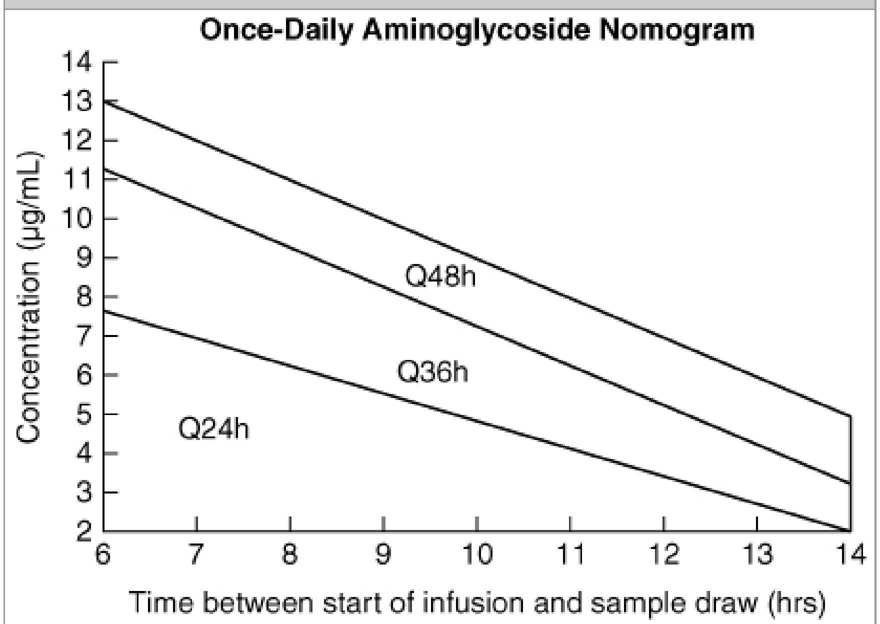
$$\text{Creatinine clearance (mL/min)} = (140 - \text{age}) \times \text{weight (kg)} \div \text{serum creatinine} \times 72$$

To monitor serum concentration, provide adequate therapeutic levels, and prevent toxicity in patients given multiple daily doses, serum aminoglycoside concentrations should be measured at two points. The first is the peak, drawn either 30 minutes after the completion of a 30-minute infusion or 1 hour after an intramuscular injection. These values for gentamicin, tobramycin, and netilmicin should be 4 to 6 μg/mL. For amikacin it should be between 20 and 30 μg/mL. The second blood sample should be drawn immediately before initiation of the next dose 7.5 or 8 hours later. Trough concentrations should be between 1 and 2 μg/mL for the first three aminoglycosides and 5 to 10 μg/mL for amikacin. These should be repeated if therapy is prolonged (3 to 4 days) or if serum creatinine levels increase. High peak and trough levels are indicators for increased risk of toxicity.

Single Daily Dosing

Increased aminoglycoside concentration enhances antibacterial activity but also toxicity. Once-daily dosing was evaluated and found to be as or less toxic than multiple daily dosing without sacrificing clinical efficacy (Bertino, 1993). Tulkens and colleagues (1988) reported that once-daily dosing of netilmicin was less toxic than administrations three times daily, without jeopardizing efficacy in the treatment of women with pelvic inflammatory disease. In 1992, Nicolau and associates presented pharmacokinetic data and a nomogram for administering aminoglycosides once daily (Fig. 3-4).

FIGURE 3-4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Once-daily aminoglycoside nomogram.

Recommendation for an initial dose, which is 7 mg/kg, is based on the patient's creatinine clearance. For those with a creatinine clearance greater than 60 mL/min, the dosing is every 24 hours. If the clearance is between 40 and 60 mL/min, the recommended dose is every 36 hours. If the clearance is less than 40 mL/min, traditional dosing is recommended.

To use the nomogram presented in Figure 3-4, one obtains a random serum concentration between 8 and 12 hours after the start

of the initial dose infusion. One then places that concentration value over the time interval to determine the dosing interval. That applies to gentamicin, tobramycin, and netilmicin. For amikacin, the initial dose is 15 mg/kg, and the resultant concentration at 8 to 12 hours should be divided by 2 and then placed on the nomogram at the dosing interval drawn.

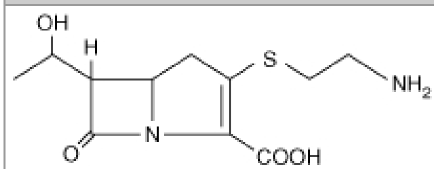
With this dosing calculation approach, standard peak and trough levels are unnecessary. A second random sample should be drawn if therapy continues for more than 4 days.

Carbapenems

STRUCTURE

The carbapenems are a third class of β-lactam antibiotics that differ from penicillins by substitution of a carbon for a sulfur atom in the five-membered ring and by the addition of a double bond therein (Fig. 3-5). The three antibiotics in this family are imipenem, meropenem, and ertapenem.

FIGURE 3-5



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Basic chemical structure of carbapenems.

ADVERSE REACTIONS

Adverse reactions are comparable to those of the other β-lactam antibiotics. As is true with other β-lactams, if patients have experienced a type 1 hypersensitivity reaction to either a penicillin or a cephalosporin, then a carbapenem should not be administered.

CLINICAL APPLICATIONS

These antibiotics are designed for polymicrobial bacterial infections, primarily those with resistant aerobic gram-negative bacteria not susceptible to other β-lactam agents. They should be reserved to preserve efficacy by preventing the development of resistance.

Monobactam

The marketed monobactam, aztreonam, is a synthetic β-lactam that has a spectrum of activity similar to aminoglycosides, that is, gram-negative aerobic species. Like other β-lactam antibiotics, these compounds inhibit bacterial cell wall synthesis by binding to penicillinâ€"binding proteins or causing cell lysis. It has affinity only for the binding proteins of the gram-negative bacteria, and does not possess affinity for either gram-positive bacteria or anaerobic organisms. For the gynecologist, aztreonam provides coverage for gram-negative aerobic bacteria, which is usually provided by aminoglycosides, in patients with significantly impaired renal function or aminoglycoside allergy.

Clindamycin

Clindamycin was introduced in the mid-1960s and has been a workhorse in the treatment of serious gynecologic infections. It is a semisynthetic derivative of lincomycin, a product of the actinomycete *Streptomyces lincolnensis.*

Clindamycin is primarily active against aerobic gram-positive bacteria and anaerobic bacteria, with little activity against aerobic gram-negative bacteria. It is also active against *Chlamydia trachomatis. Neisseria gonorrhoeae* is moderately sensitive and *Gardnerella vaginalis* is very susceptible to clindamycin. It may be delivered by one of three routes: orally, vaginally (2-percent cream), or intravenously.

The principal application of clindamycin for the gynecologist has been its combination with gentamicin and administration to women with serious community-acquired or postoperative soft tissue infections or pelvic abscess. It is also used vaginally in the treatment of women with bacterial vaginosis. Because there are parenteral and oral forms of this antibiotic, conversion from the more expensive parenteral therapy to oral therapy can occur early.

Vancomycin

Vancomycin is a glycopeptide antibiotic that is active only against aerobic gram-positive bacteria. It is primarily used by the gynecologist to treat patients in whom β-lactam therapy is impossible due to a type 1 allergic reaction. Additionally, an oral dose of 120 mg every 6 hours can be given to patients who have developed antibiotic-associated *Clostridium difficile* colitis and who do not respond to oral metronidazole.

ADVERSE REACTIONS

These are presented in Table 3-8. The most remarkable of these is the "red man" syndrome, which is a dermal reaction developing usually within minutes after initiation of a rapid drug infusion. The reaction, which is a response to histamine release, is an erythematous pruritic rash involving the neck, face, and upper torso. Hypotension also may develop. Intravenous administration over 1 hour or administration of an antihistamine may be protective, if given prior to infusion. Also associated with rapid administration may be painful back and chest muscle spasms.

Table 3-8 Vancomycin Adverse Effects
Hypersensitivity reactions Drug fever (rare) Allergic rash (rare)
Infusion-related side effects Hypotension "Red man" syndrome "Pain and spasm" syndrome
Nephrotoxicity Rare Reversible Enhanced risk with concomitant aminoglycoside therapy
Neutropenia Reversible Develops after prolonged use
Ototoxicity Hearing loss: often irreversible; rare; associated with drug levels >30 μg/mL Enhanced risk with concomitant aminoglycoside therapy

Thrombophlebitis Associated with peripheral venous cannulas

The most significant of vancomycin's side effects is nephrotoxicity, which is enhanced with aminoglycoside therapy, as is ototoxicity. Both are associated with high serum concentrations of vancomycin. For that reason, serum peak and trough concentrations are recommended, and should range between 20 and 40 µg/mL and 5 and 10 µg/mL, respectively. The initial dose should be 15 mg/kg of ideal body weight.

Metronidazole

This antibiotic was approved by the Food and Drug Administration (FDA) in the early 1960s for the treatment of trichomonal infections. Metronidazole is the principal treatment for trichomonal infections. Moreover, it is one of the mainstays of combination antimicrobial therapy given to women with serious postoperative or community-acquired pelvic infections including pelvic abscess. Since it is active only against obligate anaerobes, metronidazole must be combined with agents effective against gram-positive and gram-negative aerobic bacterial species, such as ampicillin and gentamicin. This antibiotic is also useful in treatment of bacterial vaginosis, and is as effective as vancomycin in the treatment of *C difficile* â€“associated pseudomembranous colitis.

ADVERSE REACTIONS

Up to 12 percent of patients taking oral metronidazole may have nausea, and an unpleasant metallic taste has also been described. Patients should abstain from alcohol use to avoid a disulfiram-like effect and emesis. Peripheral neuropathy and convulsive seizures have been reported, are probably dose-related, and are rare.

Fluoroquinolones

This is a new and rapidly developing antibiotic class. Also known simply as *quinolones,* these drugs have become first-line agents for treating a variety of infections because of their excellent bioavailability with oral administration, tissue penetration, broad-spectrum antibacterial activity, long half-lives, and good safety profile. As with cephalosporins, fluoroquinolones are separated into generations by their development, antibacterial activity, and pharmacokinetic properties (Table 3-9).

Table 3-9 Selected Quinolone Antibiotics

First-Generation	Second-Generation	Third-Generation
Nalidixic acid	Norfloxacin	Levofloxacin
	Ciprofloxacin	Sparfloxacin
	Ofloxacin	Clinafloxacin
	Lomefloxacin	Sitafloxacin
	Enoxacin	Gatifloxacin
	Fleroxacin	Moxifloxacin
	Pefloxacin	Gemifloxacin

ADVERSE REACTIONS

Quinolones are contraindicated in children, adolescents, and pregnant and breastfeeding women because they may affect cartilage development. As a family, they are safe, and severe adverse reactions are rare. The side effect rate ranges from 4 to 8 percent, and primarily affects the gastrointestinal (GI) tract following oral administration. Central nervous system symptoms such as headache, confusion, tremors, and seizures have been described, and these develop more frequently in patients with underlying brain

disorders.

CLINICAL APPLICATIONS

These agents are widely used by gynecologists to treat urinary tract, sexually transmitted and bacterial intestinal infections, and pelvic inflammatory disease. However, they should not be overused. If a less expensive, safer, and equally effective alternative agent is available to treat a given infection, it should be used to preserve fluoroquinolone efficacy.

PATHOGENS CAUSING GENITAL ULCER INFECTIONS

Ulceration defines complete loss of the epidermal covering with invasion into the underlying dermis, whereas *erosion* describes partial loss of the epidermis without dermal penetration. These are distinguished by clinical examination. Biopsies are generally not helpful, but may be if taken from the edge of a new lesion. Importantly, biopsy is mandatory if carcinoma is suspected (see Chap. 4, Vulvar Biopsy).

Most young sexually active women in the United States who have genital ulcers will have herpes simplex infection, syphilis, or chancroid, but some will have lymphogranuloma venereum or granuloma inguinale. Essentially all are sexually transmitted and are associated with increased risk for human immunodeficiency virus (HIV) infections. For this reason, HIV and other sexually transmitted disease testing should be offered to such patients. Sexual contacts require examination and treatment, and both require re-evaluation following treatment.

Herpes Simplex Virus Infection

Genital herpes is the most prevalent genital ulcer disease and is a chronic viral infection. The virus enters sensory nerve endings and undergoes retrograde axonal transport to the dorsal root ganglion, where the virus develops lifelong latency. Spontaneous reactivation by various events results in anterograde transport of virus particles/protein to the surface. Here virus is shed, with or without lesion formation. It is postulated that immune mechanisms control latency and reactivation (Cunningham, 2006).

There are two types of herpes simplex virus, HSV-1 and HSV-2. Type 1 HSV is the most frequent cause of oral lesions. Type 2 HSV is found more typically with genital lesions, although both types can cause genital herpes. It is estimated that 26 percent of American females age 12 and older have suffered a genital HSV-2 infection, and 40 percent of adults are seropositive to HSV-1.

Most women who have been infected with HSV-2 lack this diagnosis because of mild or unrecognized infections. Infected patients can shed infectious virus while asymptomatic, and most infections are transmitted sexually by patients that are unaware of their infection. Most (65 percent) with active infection are women.

SYMPTOMS

Patient symptoms at initial presentation will depend primarily on whether or not a patient during the current episode has antibody from previous exposure. If a patient has no antibody, the attack rate in an exposed person approaches 70 percent. The mean incubation period is about 1 week. Up to 90 percent of those who are symptomatic with their initial infection will have another episode within a year.

Burning and severe pain accompany initial vesicular lesions, and urinary symptoms such as frequency and/or dysuria may be present with those of the vulva (Fig. 3-6). The virus infects viable epidermal cells, the response to which is erythema and papule formation. With cell death and cell wall lysis, blisters form. The covering then disrupts, leaving a usually painful ulcer. These lesions develop crusting and heal, but may become secondarily infected. The three stages of lesions are: (1) vesicle with or without pustule formation, which lasts about a week; (2) ulceration; and (3) crusting. Virus is predictably shed during the first two phases of an infectious outbreak. Angiomyopathy may result from vulvar lesions, and may cause urethral obstruction. Alternatively or additionally, herpetic lesions may involve the vagina, cervix, bladder, and rectum. Commonly, a woman may have other signs of viremia such as a low-grade fever, malaise, and cephalalgia.

FIGURE 3-6

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Genital herpetic ulcers. *(Courtesy of Dr. William Griffith.)*

Viral load undoubtedly contributes to the numbers, size, and distribution of lesions. Normal host defense mechanisms inhibit viral growth, and healing starts within 1 to 2 days. Early treatment with an antiviral medication decreases the viral load.

For a previously uninfected patient, the vesicular, or initial stage, is longer. There is an increased period of new lesion formation and a longer time to healing. Pain persists for the first 7 to 10 days, and lesion healing requires 2 to 3 weeks.

If a patient has had prior exposure to HSV-2, the initial episode is significantly less severe, with shorter pain and tenderness duration, and time to healing approximates 2 weeks. Virus is shed usually only during the first week.

Recurrence following HSV-2 infection is common, and almost two thirds of patients have a prodrome prior to lesion onset. Heralding paresthesias are frequently described as pruritus or tingling in the area prior to lesion formation. However, prodromal symptoms may develop without actual lesion formation. Clinical manifestations for women with recurrences are more limited, with only about a week of symptoms.

DIAGNOSIS

The gold standard for the diagnosis of a herpetic lesion(s) is tissue culture. Specificity is high, but sensitivity is low, and declines as lesions heal. In recurrent disease, less than 50 percent of cultures are positive. Polymerase chain reaction (PCR) testing is 1.5 to 4 times more sensitive than culture and will probably replace it. Importantly, a negative culture result does not mean that there is no herpetic infection. Serologic type-specific glycoprotein Gâ€"based assays are available to detect HSV-1 and HSV-2 antibodies with a specificity ≥96 percent. The sensitivity of HSV-2 antibody testing ranges from 80 to 98 percent. Although these tests may be used to confirm herpes simplex infection, treatment and additional STD screening may be initiated in clinically obvious cases following

physical examination alone.

TREATMENT

Care Overview

Clinical management is with currently available antiviral therapy. Analgesia with nonsteroidal anti-inflammatory drugs or a mild narcotic such as acetaminophen with codeine may be prescribed. In addition, topical anesthetics such as lidocaine ointment may provide relief. Local care to prevent secondary bacterial infection is important.

Patient education is mandatory and specific topics should include the natural disease history, its sexual transmission, methods to reduce transmission, and obstetric consequences. Acquisition of this infection may have significant psychological impact, and several websites provide patient information and support. The CDC website can be accessed at http://www.cdc.gov/std/Herpes/STDFact-Herpes.htm .

Women with genital herpes should refrain from sexual activity with uninfected partners when prodrome symptoms or lesions are present. Latex condom use potentially reduce the risk for herpetic transmission.

ANTIVIRAL THERAPY

Currently available antiviral therapy includes acyclovir (Zovirax, generic); famciclovir (Famvir, Novartis, East Hanover, NJ); and valacyclovir (Valtrex, GlaxoSmithKline, Philadelphia, PA). The CDC-recommended oral medications regimens are listed in Table 3-10. Although these agents may hasten healing and decrease symptoms, therapy does not eradicate latent virus nor affect future history of recurrent infections.

Table 3-10 Recommended Oral Medication Regimens for Treatment of Genital Herpes Simplex Infection
First Clinical Episode of Genital Herpes Acyclovir 400 mg three times daily for 7 to 10 days ***or*** Acyclovir 200 mg five times daily for 7 to 10 days ***or*** Famciclovir 250 mg three times daily for 7 to 10 days ***or*** Valacyclovir 1 g twice daily for 7 to 10 days
Episodic Therapy for Recurrent Disease Acyclovir 400 mg three times daily for 5 days ***or*** Acyclovir 800 mg twice daily for 5 days ***or*** Acyclovir 800 mg three times daily for 2 days ***or*** Famciclovir 125 mg twice daily for 5 days ***or*** Famciclovir 1g twice daily for 1 day

or

Valacyclovir 500 mg twice daily for 3 days

or

Valacyclovir 1 g once daily for 5 days.

Oral Suppressive Therapy Options

Acyclovir 400 mg twice daily

or

Famciclovir 250 mg twice daily

or

Valacyclovir 0.5 to 1 g once daily

Adapted from Centers for Disease Control and Prevention, 2006, with permission.

For women with established HSV-2 infection, therapy may not be necessary if their symptoms are minimal and tolerated by the patient. Episodic therapy for recurrent disease should be initiated at least within 1 day of lesion outbreak or during the prodrome, if it exists. Ideally, patients should have medication available to begin therapy with prodromal symptoms.

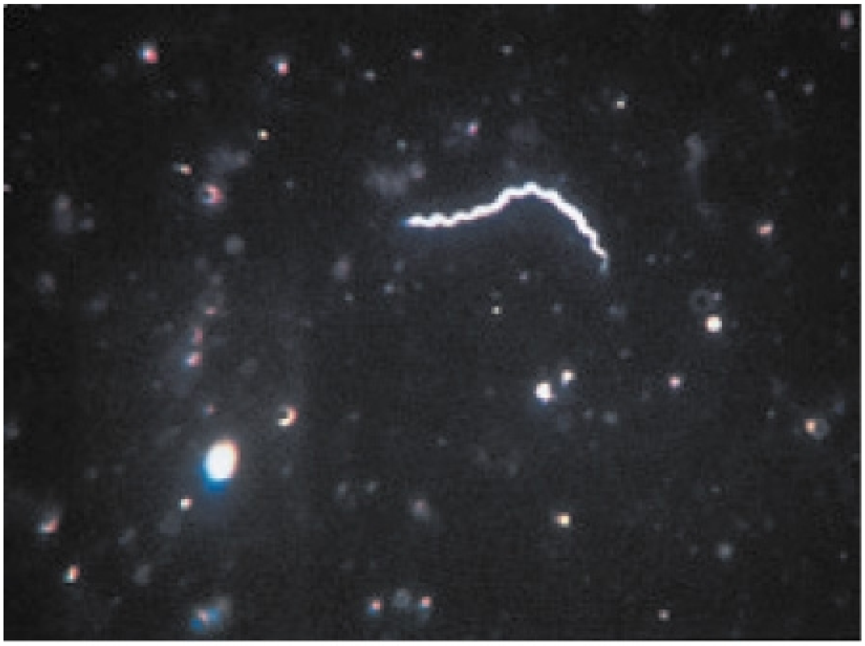
If episodes recur at intervals of 2 to 3 months, a woman may elect daily suppressive therapy, which reduces recurrences by 70 to 80 percent. Safety and efficacy data with acyclovir in such patients for up to 6 years of surveillance are available. Suppressive therapy may eliminate recurrences and decreases sexual transmission of virus by approximately 50 percent (Corey, 2004). Once-daily dosing may result in enhanced compliance and decreased cost.

Syphilis

PATHOPHYSIOLOGY

Syphilis is a sexually transmitted infection caused by the spirochete *Treponema pallidum,* which is a slender spiral-shaped organism with tapered ends (Fig. 3-7). Women at highest risk are those from lower socioeconomic groups, adolescents, those with early onset of sexual activity, and those with a large number of lifetime sexual partners. The attack rate for this infection approximates 30 percent.

FIGURE 3-7



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Microscopic views of *Treponema pallidum.* With dark-field microscopy, spirochetes appear as motile, bright corkscrews against a black background *(From Thompson, 1990, with permission).*

Primary Syphilis

The natural history of syphilis in *untreated* patients can be divided into four stages. The hallmark lesion of this infection is termed a *chancre,* in which spirochetes are abundant. Classically, it is an isolated nontender ulcer with raised rounded borders and an uninfected but integrated base. However, it may become secondarily infected and painful. Chancres are commonly found on the cervix, vagina, or vulva, but may also form in the mouth or around the anus (Fig. 3-8). This lesion may develop 10 days to 12 weeks after exposure, with a mean incubation period of 3 weeks. The incubation period is directly related to inoculum size. Without treatment, these lesions spontaneously heal in up to 6 weeks.

FIGURE 3-8

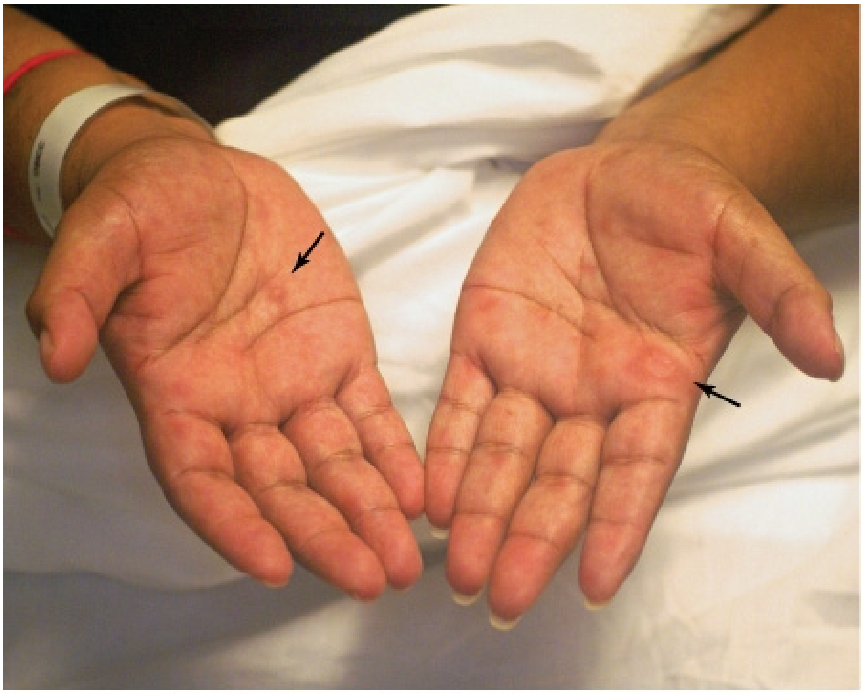
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Vulvar syphilitic chancre. *(From Wilkinson, 1995, with permission.)*

Secondary Syphilis

This phase is associated with bacteremia and develops 6 weeks to 6 months after a chancre appears. Its hallmark is a maculopapular rash that may involve the entire body and includes the palms, soles, and mucous membranes (Fig. 3-9). As is true for the chancre, this rash actively sheds spirochetes. In warm, moist body areas, this rash may produce broad, pink or gray-white, highly infectious plaques called *condylomata lata* (Fig. 3-10). Because syphilis is a systemic infection, other manifestations may include fever and malaise. Moreover, organ systems such as the kidney, liver, joints, and central nervous system (CNS) (meningitis) may be involved.

FIGURE 3-9



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photograph of a woman with multiple keratotic papules on her palms (**arrows**). With secondary syphilis, disseminated papulosquamous eruptions may be seen on the palms, soles, or trunk. *(Courtesy of Dr. William Griffith.)*

FIGURE 3-10

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photograph of a woman with multiple condyloma lata on her labia. Soft, flat, moist, pink-tan papules and nodules on the perineum and perianal area are typical of this dermal manifestation of secondary syphilis. *(Courtesy of Dr. William Griffith.)*

Latent Syphilis

During the first year following secondary syphilis without treatment, termed *early latent syphilis,* secondary signs and symptoms may recur. However, lesions associated with these outbreaks are not usually contagious. *Late latent syphilis* is defined as a period greater than 1 year after the initial infection.

Tertiary Syphilis

This phase of untreated syphilis may appear up to 20 years after latency. During this phase, cardiovascular, CNS, and musculoskeletal involvement become apparent. However, cardiovascular and neurosyphilis are half as common in females as in males.

DIAGNOSIS

Early syphilis is diagnosed primarily by dark-field examination or direct fluorescent antibody testing of lesion exudate. In the absence of this positive diagnosis, presumptive diagnosis may be reached with serologic tests that are nontreponemal: (1) Venereal Disease Research Laboratory (VDRL) or (2) rapid plasma reagin (RPR) tests (Table 3-11). Alternatively, treponemal-specific tests may be selected: (1) fluorescent treponemal antibody-absorption (FTA-ABS) or (2) *Treponema pallidum* particle agglutination (TP-PA) tests. Clinicians should be familiar with the uses of syphilis serologic tests. For population screening, RPR or VDRL testing is appropriate. For quantitative measurement of antibody titers to assess response to treatment, RPR or VDRL tests are typically used. But for diagnosis confirmation in a woman with a positive nontreponemal antibody test result or with a suspected clinical diagnosis, then FTA-ABS or TP-PA testing should be selected.

Table 3-11 Sensitivity of Serodiagnostic Tests in Untreated Syphilis

	Mean Percentage Positive (Range) at Indicated Stage of Disease[b]			
Test[a]	**Primary**	**Secondary**	**Latent**	**Tertiary**
VDRL, RPR	78 (74â€“87)	100	95 (88â€“100)	71 (37â€“94)
FTA-ABS	84 (70â€“100)	100	100	96
TP-PA[c]	89	100	100	NA

FTA-ABS = fluorescent treponemal antibody-absorption; NA = not available; RPR = rapid plasma reagin; VDRL = Venereal Disease Research Laboratory; TP-PA = *Treponema pallidum* particle agglutination.

[a] The specificity for each of these tests is 94 to 99 percent.

[b] In CDC studies.

[c] Limited numbers of sera have been evaluated by TP-PA.

From Lukehart, 2007, with permission.

Following treatment, sequential nontreponemal tests should be performed. A fourfold titer decrease (two dilutions) is required to define a clinically significant decline. During surveillance, the same type test should be used. These tests usually become nonreactive after treatment and with time. However, some women may have a persistent low rating, and these patients are described as *serofast* . Women with a reactive treponemal-specific test will more than likely have a positive test for the remainder of their lives, but up to 25 percent may revert to a negative result after several years.

TREATMENT

Since 1943, penicillin has been the first-line therapeutic agent for this infection, and benzathine penicillin is primarily chosen. Specific recommendations for therapy by the CDC (2006) are listed in Table 3-12. With treatment, an acute, self-limited febrile response, termed a *Jarisch-Herxheimer reaction,* may develop within the first 24 hours after treatment of early disease and is associated with headache and myalgia.

Table 3-12 Recommended Treatment of Syphilis

Primary, secondary, early latent (<1 year) syphilis
Recommended regimen:
Benzathine penicillin G, 2.4 million units IM once
Alternative oral regimens (penicillin-allergic, nonpregnant women):
Doxycycline 100 mg orally twice daily for 2 weeks
or
Tetracycline 500 mg orally four times daily for 2 weeks
Late latent, tertiary, and cardiovascular syphilis
Recommended regimen:
Benzathine penicillin G, 2.4 million units IM weekly times 3 doses

Alternative oral regimen (penicillin-allergic, nonpregnant women):
Doxycycline 100 mg orally twice daily for 4 weeks

From Centers for Disease Control and Prevention, 2006, with permission.

As with other STDs, all patients treated for syphilis should be tested for other STDs. Patients with evidence of neurologic or cardiac involvement should be treated by an infectious disease specialist. After initial treatment, women should be seen at 6-month intervals for clinical evaluation as well as serologic retesting. A four fold dilution decrease is anticipated. If this does not occur, a patient has either failed treatment or was re-infected and should be re-evaluated and retreated. Retreatment recommendations are benzathine penicillin G, 2.4 million units IM weekly for 3 weeks.

Alternative treatment to intramuscular penicillin involves regimens with oral tetracyclines. Thus, if patients with penicillin allergy cannot be followed or if their compliance is questioned, then skin testing, desensitization, and treatment with IM benzathine penicillin is recommended (Wendel Jr., 1985).

Chancroid

Chancroid is one of the classical sexually transmitted diseases, but is an uncommon infection in the United States. It appears as local outbreaks predominantly in black and Hispanic males.

It is caused by a nonmotile, nonspore-forming, facultative, gram-negative bacillus, *Haemophilus ducreyi.* Incubation usually spans 3 to 10 days, and host access probably requires a break in the skin or mucous membrane. Chancroid does not cause a systemic reaction, and no prodromal syndrome precedes the appearance of infection.

SYMPTOMS

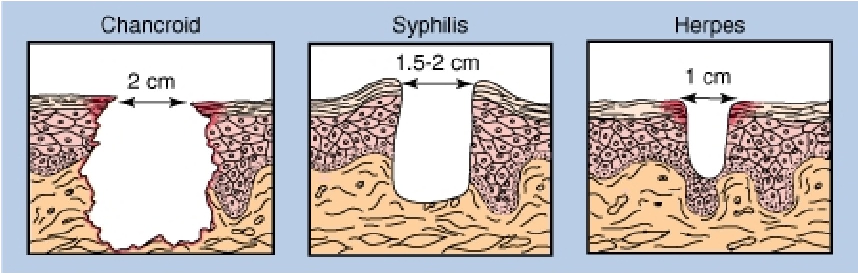
This disease presents initially as an erythematous papule that becomes pustular and within 48 hours, ulcerates. Edges of these painful ulcers are usually irregular with erythematous nonindurated margins. The ulcer bases are usually red and granular, and in contrast to a syphilitic chancre, are typically soft. Lesions are frequently covered with purulent material, and if secondarily infected, a foul odor will result.

The most common locations in women include the fourchette, vestibule, clitoris, and labia. Ulcers on the cervix or vagina may be nontender. Concurrently, approximately half of patients will develop unilateral or bilateral tender inguinal lymphadenopathy. If large and fluctuant, they are termed *buboes* . These may occasionally suppurate and form fistulas, the drainage from which will result in other ulcer formation.

DIAGNOSIS

The diseases most commonly imitating this presentation are syphilis and genital herpes (Fig. 3-11). These may co-exist, but uncommonly.

FIGURE 3-11



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Drawing depicts the differences in clinical appearance among chancroid, syphilis, and genital herpes. These are the three most common infectious diseases manifested by genital ulcers. *(From Schmid, 1990, with permission.)*

Definitive diagnosis requires growth of *H ducreyi* on special media, but sensitivity for culture is less than 80 percent. A presumptive diagnosis can be made with identification of gram-negative, nonmotile rods on a Gram stain of lesion contents. Before obtaining either specimen, superficial pus or crusting should be removed with sterile, saline-soaked gauze.

TREATMENT

The CDC's (2006) recommended regimens for nonpregnant women are found in Table 3-13. Successful treatment will result in symptomatic improvement within 3 days, and objective evidence of improvement within 1 week. Lymphadenopathy resolves more slowly, and if fluctuant, incision and drainage may be warranted. Those with co-existing HIV infection may require longer therapy courses, and treatment failures are more common. Accordingly, some recommend longer regimens for initial management of known HIV-infected patients.

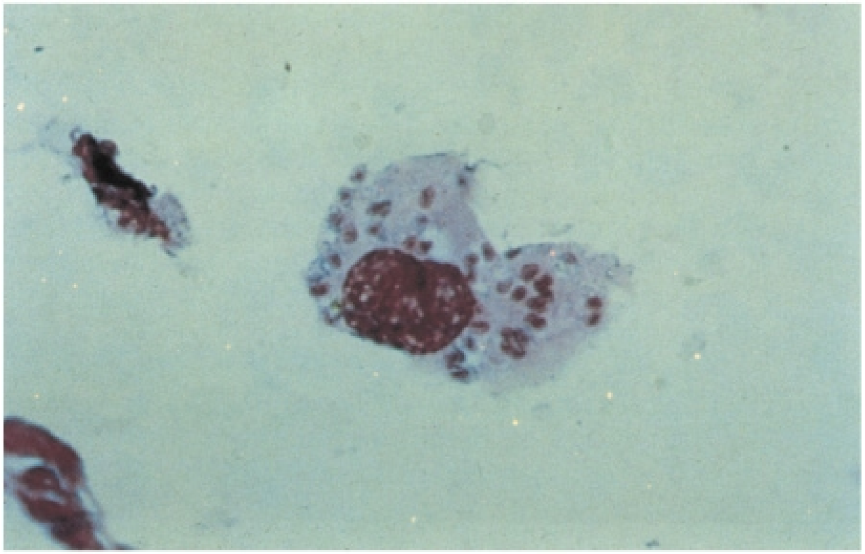
Table 3-13 Recommended Treatment of Chancroid
Azithromycin 1 g orally
or
Ceftriaxone 250 mg intramuscularly
or
Ciprofloxacin 500 mg orally twice daily for 3 days
or
Erythromycin base 500 mg orally three times daily for 7 days

From Centers for Disease Control and Prevention, 2006, with permission.

Granuloma Inguinale

Granuloma inguinale genital ulcerative disease is also known as donovanosis, and is caused by the intracellular gram-negative bacterium *Calymmatobacterium (Klebsiella) granulomatis.* This bacterium is encapsulated and has a characteristic appearance in tissue biopsy or cytology specimens (Fig. 3-12). Apparently this disease is only mildly contagious, requires repeated exposures, and has a long incubation period of weeks to months.

FIGURE 3-12



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photomicrograph of a mononuclear cell containing Donovan bodies. Wright-Giemsa staining creates a "closed safety pin" appearance. *(From Kellogg, 1990, with permission.)*

SYMPTOMS

Granuloma inguinale presents as painless inflammatory nodules that progress to highly vascular, beefy red ulcers that bleed easily on contact. If secondarily infected they may become painful. These ulcers heal by fibrosis, which can result in scarring resembling keloids. Lymph nodes are usually uninvolved, but may become enlarged, and new lesions may appear along these lymphatic drainage channels. Distant lesions have also been reported.

DIAGNOSIS

Diagnosis is confirmed by identification of Donovan bodies during microscopic evaluation of a specimen following Wright-Giemsa staining. Currently, there are no FDA-approved PCR tests for *C granulomatis* DNA.

TREATMENT

Treatment does stop lesion progression and may be lengthy without formation of granulation tissue in ulcer bases and re-epithelialization (Table 3-14). Relapses have been reported up to 18 months after "effective" treatment. A few prospective treatment trials have been published, but these are limited. If successful, improvement will be evident within the first few days of treatment.

Table 3-14 Recommended Treatment of Granuloma Inguinale
Doxycycline 100 mg twice daily for a minimum of 3 weeks and until lesions have completely healed
or
Azithromycin 1 g orally once a week as above
or
Ciprofloxacin 750 mg orally twice daily as above
or
Erythromycin base 500 mg orally four time daily as above
or
Trimethoprim-sulfamethoxazole DS orally twice daily as above

DS = double strength.

From Centers for Disease Control and Prevention, 2006, with permission.

Lymphogranuloma Venereum (LGV)

This ulcerative genital disease is caused by *Chlamydia trachomatis,* serotypes L1, L2, and L3. Lymphogranuloma venereum (LGV) is uncommon in the United States. As is true with other sexually transmitted diseases, this infection is found in lower socio-economic groups among sexually promiscuous persons.

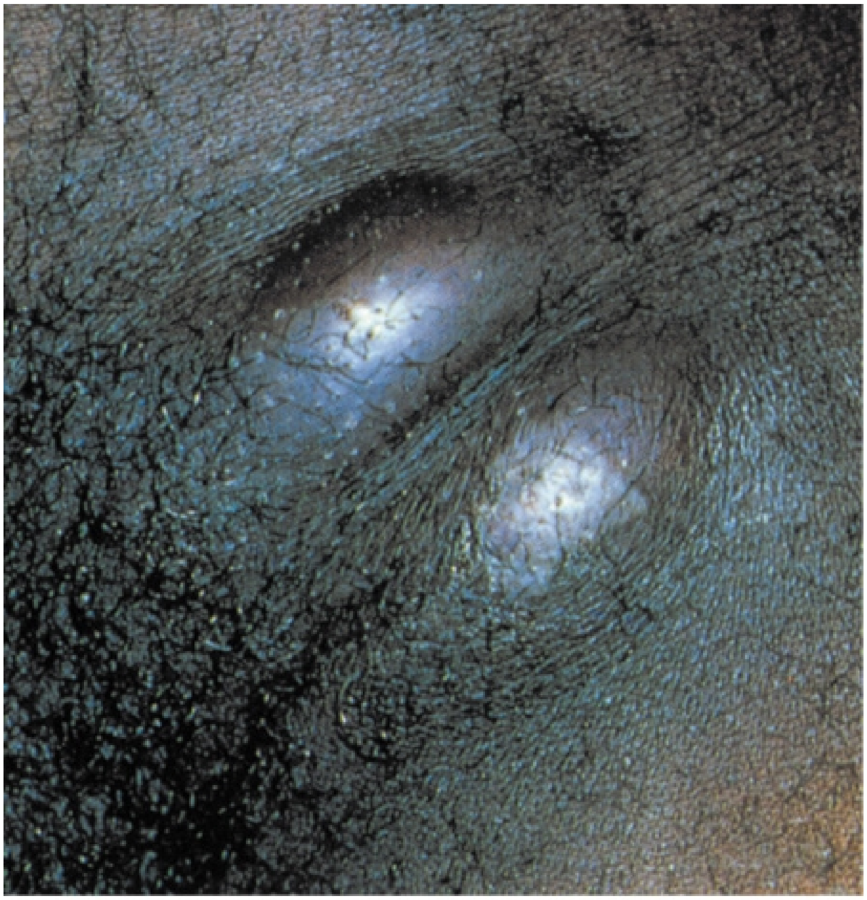
The chlamydial life cycle is comprised of three stages. Initially, infective particles (elementary bodies) penetrate a host cell. Here they develop into metabolically active reticulate bodies. Binary fission within the cell allows reticulate bodies to transform themselves into multiple elementary bodies, which are released by exocytosis.

SYMPTOMS

This infection is commonly divided into three stages as follows: stage 1â€”small vesicle or papule; stage 2â€”inguinal or femoral lymphadenopathy; and stage 3â€”anogenitorectal syndrome. Incubation for this infection ranges from 3 days to 2 weeks. Initial papules heal quickly and without scarring. They appear primarily on the fourchette and posterior vaginal wall up to and including the cervix. Repeated inoculation may result in lesions at multiple sites.

During the second stage, sometimes referred to as the *inguinal syndrome,* progressive enlargement of inguinal and femoral lymph nodes is observed. Enlarged painful nodes can mat together and create a characteristic "groove sign", which appears in up to one fifth of infected women (Fig. 3-13). In addition, enlarging nodes may rupture through the skin, and chronically draining sinuses may result. Fever may be noted prior to rupture. Commonly, women with LGV develop systemic infection with chlamydia and manifest malaise and fever. Additionally, pneumonitis, arthritis, and hepatitis have been reported with this infection.

FIGURE 3-13



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photograph of the "groove sign" seen with lymphogranuloma venereum. Enlarged lymph nodes matted together on either side of the inguinal ligament create this characteristic groove. *(From Barnes, 1990, with permission.)*

In the third stage of LGV, a patient develops rectal pruritus and a mucoid discharge from rectal ulcers. If these become infected, the discharge becomes purulent. This presentation is a result of lymphatic obstruction that follows lymphangitis and that may result in elephantiasis of external genitalia initially and fibrosis of the rectum. Rectal bleeding is common, and a woman may complain of crampy, abdominal pain with abdominal distention, rectal pain, and fever. Peritonitis may follow bowel perforation. Stenosis of the urethra and the vagina has also been reported.

DIAGNOSIS

Lymphogranuloma venereum may be diagnosed following clinical evaluation with exclusion of other etiologies and positive chlamydial testing. A serologic titer that is greater than 1:64 can support the diagnosis. Additionally, lymph node specimens obtained by swab or aspiration may be cultured for *C trachomatis* or tested by immunofluorescence or PCR.

TREATMENT

The 2006 CDC-recommended regimen is doxycycline, 100 mg orally twice daily for 21 days. Alternatively, one may use erythromycin base, 500 mg orally four times daily, for the same duration. It is recommended that sexual contacts exposed to a patient within the prior 60 days should be tested for urethral or cervical infection, and treated with either standard antichlamydial regimen.

PATHOGENS CAUSING INFECTIOUS VAGINITIS

The term *vaginitis* is the diagnosis given to women who present complaining of abnormal vaginal discharge with vulvar burning, irritation, or itching. It is one of the most frequent reasons for patient visits to the gynecologist (American College of Obstetricians and Gynecologists, 2006). The leading causes of symptomatic vaginal discharge are bacterial vaginosis, candidiasis, and trichomoniasis.

Between 7 and 70 percent of women who have vaginal discharge complaints will have no definitive diagnosis (Anderson, 2004). For those in whom identifiable infection is absent, an inflammatory diagnosis and treatment for infection should not be given. In such instances, a woman may seek reassurance, having concern about a recent sexual exposure, and sexually transmitted disease testing may alleviate this. Importantly, during evaluation, a clinician should obtain a complete history regarding prior vaginal infections and their treatment; duration of symptoms; whether or not the patient has used over-the-counter (OTC) preparations, and if so which type and when; and a complete menstrual and sexual history. Moreover, a thorough physical examination of the vulva, vagina, and cervix should be performed. Several etiologies may be identified in the office by microscopic examination of a vaginal specimen (wet prep), and vaginal pH analysis may add supportive information (Table 3-15). Unfortunately, inexpensive laboratory testing is not as accurate as a clinician would hope (Bornstein, 2001; Landers, 2004).

Table 3-15 Summary of Characteristics of Common Vaginal Infections

Category	**Physiologic (normal)**	**Bacterial Vaginosis**	**Candidiasis**	**Trichomoniasis**	**Bacterial (streptococcal, staphylococcal, *E coli*)**
Chief complaint	None	Bad odor, increased after intercourse	Itching, burning, discharge	Frothy discharge, bad odor, dysuria, pruritis, spotting	Thin, watery discharge, pruritis
Discharge	White, clear	Thin, gray or white, adherent, often increased	White "cottage cheese like" discharge	Green-yellow, frothy, adherent, increased	Purulent
KOH "whiff test"	Absent	Present (fishy)	Absent	May be present	Absent
Vaginal pH	3.8â€“4.2	>4.5	<4.5	>4.5	>4.5
Microscopic findings	N/A	"Clue cells", slight increase in WBCs, clumps of bacteria (saline wet mount)	Hyphae and buds in 10-percent KOH solution (wet mount)	*Trichomonads* (protozoa with 3-5 flagella) may be seen moving on saline wet mount	Many WBCs

E coli = *Escherichia coli;* KOH = potassium hydroxide; N/A = not applicable; WBC = white blood cell.

Fungal Infection

This infection is most commonly caused by *Candida albicans,* which can be found in the vagina of asymptomatic patients, and is a commensal of the mouth, rectum, and vagina. Candidiasis is seen more commonly in warmer climates and in obese patients. Additionally, immunosuppression, diabetes mellitus, pregnancy, and recent broad-spectrum antibiotic use predispose women to clinical infection. It can be sexually transmitted, and several studies have reported an association between candidiasis and orogenital sex (Bradshaw, 2005; Geiger, 1996).

DIAGNOSIS

Symptoms of candidiasis include pruritus, pain, and swelling. In addition, vulvar erythema and edema with excoriations are common findings (Fig. 3-14). The typical vaginal discharge is described as a cottage cheese-like discharge. Vaginal pH is normal

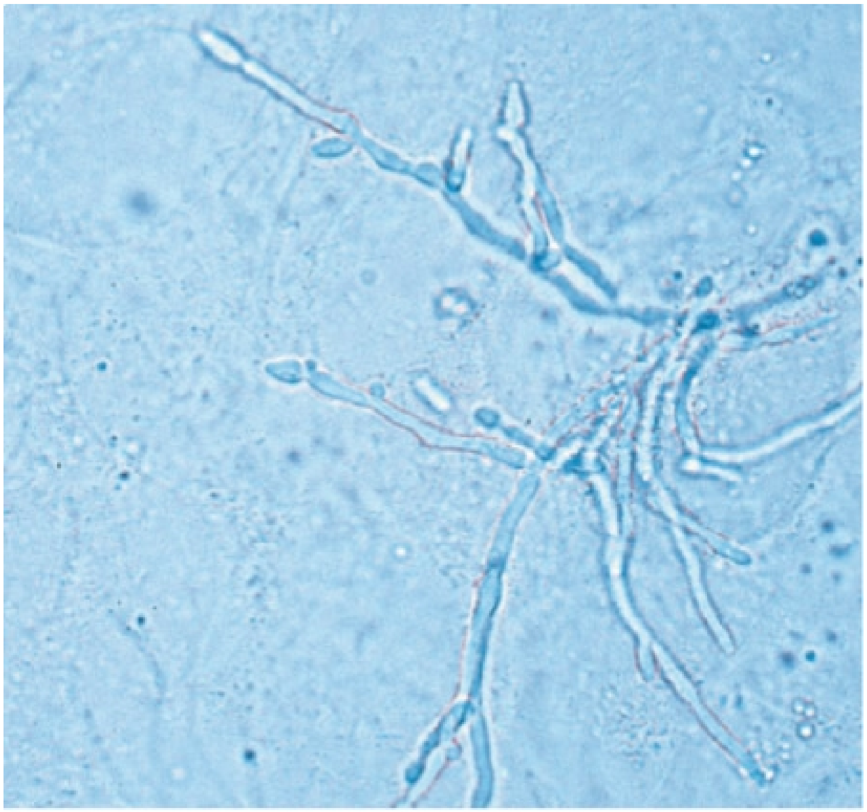
(less than 4.5) and microscopic examination of vaginal discharge with saline and 10-percent KOH allows yeast identification (Fig. 3-15). *Candida albicans* is dimorphic with both yeast buds and hyphal forms. It may be present in the vagina as a filamentous fungus (pseudohyphae) or as germinated yeast with mycelia. Vaginal candidal culture is not routinely recommended. However, it may be warranted for those who fail empiric treatment and for women with evidence of infection, yet absence of microscopic yeast.

FIGURE 3-14

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Thick white discharge, labial erythema, and edema are seen with candidiasis. *(Courtesy of Dr. William Griffith.)*

FIGURE 3-15



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Micrograph of *Candida albicans* in a potassium hydroxide preparation. Serpentine pseudohyphae are seen. *(From Hansfield, 1992, with permission.)*

TREATMENT

The CDC vulvovaginal candidiasis classification (2006) is presented in Table 3-16. Various treatment formulations that are effective in treating both uncomplicated and complicated infection are presented in Table 3-17. For uncomplicated infection, azoles are extremely effective, but women should be encouraged to return if therapy is unsuccessful.

Table 3-16 Vulvovaginal Candidiasis Classification
Uncomplicated
• Sporadic or infrequent
and
• Mild to moderate
and
• Likely infecting agent is *Candida albicans*
and
• Nonimmunocompromised woman
Complicated
• Recurrent candidal infection
or
• Severe infection
or
• Non-*albicans* candidiasis (*C tropicalis, C glabrata,* etc.)
or
• Uncontrolled diabetes, immunosuppression, debilitation, pregnancy

From Centers for Disease Control and Prevention, 2006, with permission.

Table 3-17 Recommended Treatment of Vulvovaginal Candidal Infection
Intravaginal agents
Butoconazole 2% cream
5 g intravaginally for 3 days[a]
or
5 g (sustained-release) once
or
Clotrimazole
1% cream, 5 g intravaginally 7 to 14 days[a]
or

100 mg tablet intravaginally for 7 days
or
100 mg tablet intravaginally, 2 tablets for 3 days
or
Miconazole
2% cream, 5 g intravaginally for 7 days[a]
or
100 mg suppository intravaginally for 7 days[a]
or
200 mg suppository intravaginally for 3 days[a]
or
1200 mg suppository intravaginally once[a]
or
Nystatin 100,000-unit tablet intravaginally for 14 days
or
Tioconazole 6.5% ointment, 5 g intravaginally once[a]
or
Terconazole
0.4% cream, 5 g intravaginally for 7 days
or
0.8% cream, 5 g intravaginally for 3 days
or
80-mg suppository intravaginally for 3 days
Oral agent
Fluconazole 150 mg oral tablet once

[a] Over-the-counter preparations

From Centers for Disease Control and Prevention, 2006, with permission.

Women who have four or more candidal infections during a year are classified as having complicated disease, and cultures should

be obtained to confirm the diagnosis. Non-*albicans* candidal species are not as responsive to topical azole therapy. Therefore, prolonged local intravaginal therapy regimens and addition of oral fluconazole, one to three times a week, may be required to achieve clinical cure. Primary treatment for prevention of recurrent infection is oral fluconazole, 100 to 200 mg weekly for 6 months. For non-*albicans* recurrent infection, a 600-mg boric acid gelatin capsule intravaginally daily for 2 weeks has been successful.

Oral azole therapy has been associated with elevation in liver enzymes. Thus, prolonged oral therapy may not be feasible for that reason or because of interactions with other patient medications such as calcium channel blockers, warfarin, protease inhibitors, trimetrexate, terfenadine, cyclosporine A, phenytoin, and rifampin. In these cases, local intravaginal therapy once or twice weekly may give a similar clinical response.

Trichomoniasis

EPIDEMIOLOGY

This infection is the most prevalent nonviral STD in the United States (Van der Pol, 2005, 2007). Unlike other STDs, its incidence appears to increase with age in some studies. Trichomoniasis is more commonly diagnosed in women because most men are asymptomatic. However, up to 70 percent of male partners of women with vaginal trichomoniasis will have trichomonads in their urinary tract.

This parasite is usually a marker of high-risk sexual behavior, and co-infection with other sexually transmitted pathogens is common, especially *Neisseria gonorrhoeae. Trichomonas vaginalis* has predilection for squamous epithelium, and lesions may increase accessibility to other sexually transmitted species. Vertical transmission during birth is possible and may persist for a year.

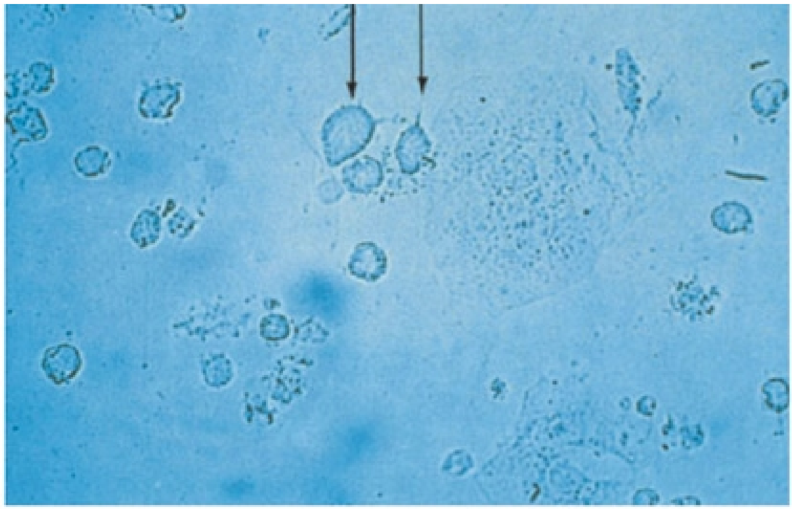
DIAGNOSIS

Incubation with *T vaginalis* requires 3 days to 4 weeks, and the vagina, urethra, endocervix, and bladder can be infected. No symptoms may be noted in up to one-half of women with trichomoniasis, and such colonization may persist for months or years in some women. However, in those with complaints, vaginal discharge is typically described as foul, thin, and yellow or green. Additionally, dysuria, dyspareunia, vulvar pruritus, and pain may be noted. At times, symptomatology and physical findings are identical to those of acute pelvic inflammatory disease.

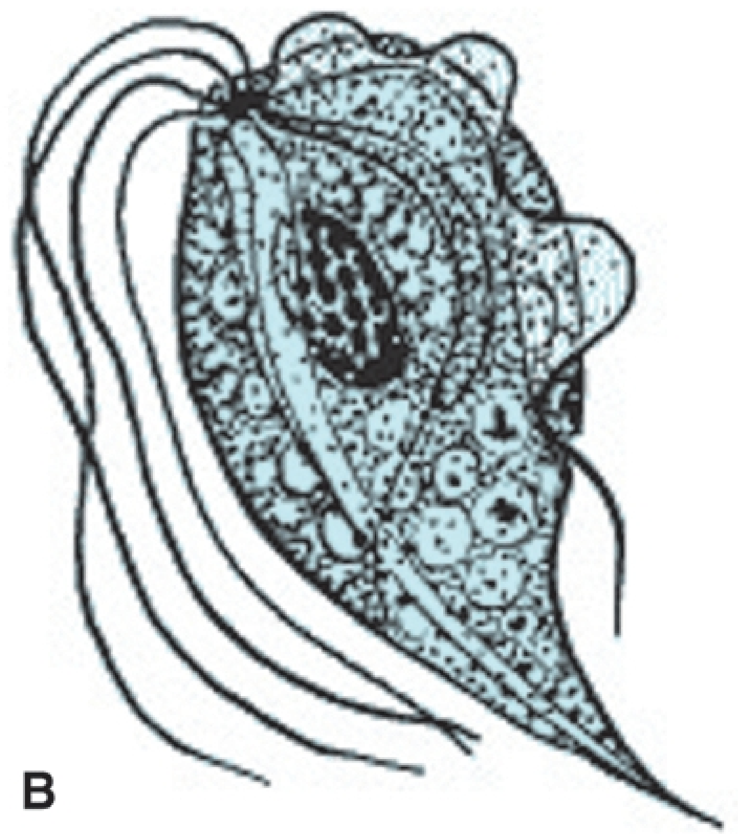
With trichomoniasis, the vulva may be erythematous, edematous, and excoriated. The vagina contains the above-described discharge, and subepithelial hemorrhages or "strawberry spots" may be seen on the vagina and cervix. Trichomoniasis is typically diagnosed by microscopic identification of parasites in a saline preparation of the discharge. Trichomonads are anteriorly flagellated, and therefore mobile, anaerobic protozoa. They are oval and slightly larger than a white blood cell (WBC) (Fig. 3-16). Trichomonads become less motile with cooling, and slides should be read within 20 minutes. Inspection of a saline preparation is highly specific, yet sensitivity is not as high as hoped (60 to 70 percent). In addition to microscopy, vaginal pH is often elevated.

FIGURE 3-16

A



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Trichomonads. **A.** Photomicrograph of a vaginal smear saline preparation containing trichomonads (**arrows**). *(From Hansfield, 1992, with permission.)* **B.** Drawing depicts anatomic features of trichomonads. Flagella allow this parasite to be motile. *(From Brooks, 2004, with permission.)*

The most sensitive diagnostic technique is culture, which is impractical because special media (Diamond media) is required and few laboratories are equipped. Moreover, nucleic acid amplification tests (NAAT) for trichomonal DNA are sensitive and specific, but not widely available. Alternatively, the OSOM Trichomonas Rapid Test (Genzyme, Cambridge, MA) is an immunochromatographic assay, which has 88 percent sensitivity and 99 percent specificity. It is available for office use, and results are available in 10 minutes (Huppert, 2005). Trichomonads may also be noted on Pap smear screening and sensitivity approximates 60 percent.

Women with trichomonal infection should be tested for other sexually transmitted infections. Additionally, sexual contact(s) should be evaluated or referred for evaluation.

TREATMENT

Oral regimens recommended by the CDC (2006) are found in Table 3-18. Although each is effective, some report that a 7-day treatment regimen with metronidazole may be more effective in compliant patients. However, compliance may be poor because of longer treatment length and metronidazole side effects. Adverse effects may include a metallic taste and a disulfiram-like reaction if combined with alcohol. Accordingly, patients should abstain from alcohol during use and for 24 hours following metronidazole therapy and for 72 hours after tinidazole (Tindimax, Mission Pharmacal, San Antonio, TX).

Table 3-18 Recommended Treatment of Trichomoniasis
Primary therapy
Metronidazole single 1-g dose orally
or
Tinidazole single 2-g dose orally
Alternative regimen
Metronidazole 500 mg orally twice daily for 7 days

From Centers for Disease Control and Prevention, 2006, with permission.

Patients who become asymptomatic or who are asymptomatic do not require routine re-evaluation. However, recurrence occurs in approximately 30 percent of patients. Condom use may be protective.

There are infrequent patients who have strains that are highly resistant to metronidazole, but these organisms are usually sensitive to tinidazole. Culture and sensitivity should be performed on specimens from patients with frequently recurring infections or from those who do not respond to the initial therapy and who are medication compliant. Oral tinidazole at doses of 500 mg orally three times daily for 7 days or four times daily for 14 days have been effective in curing patients with resistant organisms (Sobel, 2001).

PATHOGENS CAUSING SUPPURATIVE CERVICITIS

Neisseria gonorrhoeae

Gonococcal infections among women are frequently asymptomatic. For that reason, it is essential that women at risk be screened periodically (see Table 1-2). Risk factors for gonococcal carriage and potential upper reproductive tract infection are: age less than 25 years, the presence of other sexually transmitted infections, a history of previous gonococcal infection, new or multiple sexual partners, lack of barrier protection, drug use, and commercial sex work. Screening for women at low risk is not recommended (U.S. Preventive Services Task Force, 2005).

SYMPTOMS

Symptomatic gonorrhea may present as vaginitis or cervicitis. Those with cervicitis commonly describe a profuse odorless, nonirritating, and white-to-yellow vaginal discharge. Gonococcus can also infect the Bartholin and Skene glands, the urethra, and ascend into the endometrium and fallopian tube to cause upper reproductive tract infection (Microbiology and Pathogenesis).

DIAGNOSIS

Neisseria gonorrhoeae is a gram-negative coccobacillus that invades columnar and transitional epithelial cells, becoming intracellular. For this reason, the vaginal epithelium is not involved. For gonococcal identification, NAATs are available, and ideal specimens are recovered from the endocervix. These tests have replaced culture in most laboratories. However, these noncultural tests are not FDA-cleared for diagnostic identification of rectal or pharyngeal disease.

All patients tested for gonorrhea should be tested for other sexually transmitted infections, and sexual contacts should be evaluated or referred for evaluation and treatment. Abstinence should be practiced until therapy is completed and until they and their sexual partners have resolution of symptoms.

TREATMENT

Recommendations for single-dose therapy of uncomplicated cervical, urethral, or rectal infection by the CDC is outlined in Table 3-19. Uncomplicated gonococcal pharyngeal infections can be treated with either the ceftriaxone or ciprofloxacin regimens listed. Quinolone-resistant gonococci are increasing in the U.S., particularly the east and west coast. Those strains are common in Europe, the Middle East, the Pacific, and Asia. For that reason, the CDC has advised against quinolone use in California, Hawaii, and for travelers who have been to the listed countries. Test-of-cure cultures are not necessary; however, re-infection is common. Some recommend retesting 3 months following initial therapy.

Table 3-19 Recommended Single-Dose Treatment of Uncomplicated Gonococcal Infection of the Cervix, Urethra, or Rectum
Ceftriaxone 125 mg IM
or
Cefixime 400 mg orally
or
Ciprofloxacin 500 mg orally
or
Ofloxacin 400 mg orally
or
Levofloxacin 250 mg orally
plus
Treatment for chlamydial infection if not excluded

From Centers for Disease Control and Prevention, 2006, with permission.

Chlamydia trachomatis

This organism is the second most prevalent of the sexually transmitted disease species recovered in the United States, and its highest prevalence is found in individuals younger than 25 years. Since many with this organism are asymptomatic, annual screening of sexually active women younger than 25 years and those at risk is recommended (see Table 1-2).

SYMPTOMS

This obligate intracellular parasite is dependent on host cells for survival (Lymphogranuloma Venereum (LGV)). It causes columnar epithelial infection. Thus presenting symptoms reflect endocervical glandular infection, with resultant mucopurulent discharge or

endocervical secretions. If infected, the endocervical tissue is commonly edematous and hyperemic. Urethritis is another lower genital tract infection that can develop, and dysuria is prominent.

DIAGNOSIS

Microscopic inspection of secretions following a saline preparation typically reveals 20 or more leukocytes per high-power field. More specifically, culture, NAAT, and enzyme-linked immunosorbent assay (ELISA) are available for endocervical specimens. Alternatively, a combined gonococcal and chlamydial test is widely used. If *C trachomatis* is diagnosed or suspected, then screening for other STDs is indicated. Moreover, sexual partner(s) should be counseled, tested, and treated or referred for evaluation.

TREATMENT

Recommended therapy for *C trachomatis* infection is described in Table 3-20. Azithromycin has the obvious therapeutic compliance advantage of allowing clinicians to observe ingestion at the time of diagnosis. Following treatment, retesting is not recommended if symptoms resolve. To prevent further infection, abstinence is recommended until a woman and her partner(s) are asymptomatic.

Table 3-20 Recommended Treatment of Chlamydial Infection
Primary treatment
Azithromycin 1 g orally once
or
Doxycycline 100 mg orally twice daily for 7 days
Alternative regimens
Erythromycin base 500 mg orally four times daily for 7 days
or
Erythromycin ethyl succinate 800 mg orally four times daily for 7 days
or
Ofloxacin 300 mg orally twice daily for 7 days
or
Levofloxacin 500 mg orally daily for 7 days

From Centers for Disease Control and Prevention, 2006, with permission.

PATHOGENS CAUSING MASS LESIONS

External Genital Warts

These lesions are created from productive infection with the human papillomavirus (HPV), and a fuller discussion of the pathophysiology of this virus is found in Chapter 29, Human Papillomavirus. Genital warts display differing morphologies, and appearances range from flat papules to the classic verrucous, exophytic lesions, termed *condyloma acuminata* (Fig. 3-17) (Beutner, 1998). Involved tissues vary and external genital warts may develop at sites in the lower reproductive tract, urethra, anus, or mouth. They are typically diagnosed by clinical inspection, and biopsy is not required unless co-existing neoplasia is suspected (Beutner, 1998; Wiley, 2002). Similarly, HPV serotyping is not required for routine diagnosis.

FIGURE 3-17

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photograph of vulvar condyloma acuminata. Multiple exophytic verrucous warts are seen. *(Courtesy of Dr. Claudia Werner.)*

TREATMENT

Condyloma acuminata may remain unchanged or spontaneously resolve, and the effect of treatment on future viral transmission is unclear (Centers for Disease Control and Prevention, 2006). However, many women prefer removal, and lesions can be destroyed with sharp or electrosurgical excision, cryotherapy, or laser ablation. In addition, very large, bulky lesions may be managed with cavitational ultrasonic surgical aspiration (see Chap. 40, Cavitational Ultrasonic Surgical Aspiration).

Alternatively, 5-percent imiquimod cream (Aldara, 3M, St. Paul, MN) is a patient-applied immunomodulatory topical treatment for genital warts. This agent induces macrophages to secrete several cytokines, and of these, interferon-γ is probably the most important. For genital wart clearance, this cytokine stimulates a cell-mediated immune response against HPV (Scheinfeld, 2006). Other topical agents may be applied for treatment of warts (Table 3-21). Of these, podophyllin is an antimitotic agent available in a 10- to 25-percent tincture of benzoin solution and disrupts viral activity by inducing local tissue necrosis. A biologically active extract of podophyllin, *podofilox,* also termed *podophyllotoxin,* is available in a 0.5-percent solution or gel (Condylox, Watson Pharma, San Antonio, TX), which can be self-applied by the patient. Alternatively, trichloroacetic acid and bichloroacetic acid are proteolytic agents and are applied serially to warts by clinicians. Intralesion injection of interferon is an effective treatment for warts (Eron, 1986). However, because of high cost and painful and inconvenient administration, this therapy is not recommended as a primary modality and is best reserved for recalcitrant cases (Centers for Disease Control and Prevention, 2006).

Table 3-21 Recommended Treatment of External Genital Warts
Patient-applied:
Podofilox 0.5% solution or gel. Patients should apply podofilox solution with a cotton swab, or podofilox gel with a finger, to visible genital warts twice a day for 3 days, followed by 4 days of no therapy. This cycle may be repeated, as necessary, for up to four cycles. The total wart area treated should not exceed 10 cm^2 , and the total volume of podofilox should be limited to 0.5 mL per day.
or
Imiquimod 5% cream. Patients should apply imiquimod cream once daily at bedtime, three times a week for up to 16 weeks. The treatment area should be washed with soap and water 6 to 10 hours after the application.
Provider-administered:
Cryotherapy with liquid nitrogen or cryoprobe. Repeat applications every 1 to 2 weeks.
or
Podophyllin resin 10 to 25 percent in a compound tincture of benzoin. A small amount should be applied to each wart and allowed to air dry. The treatment can be repeated weekly, if necessary. Application should be limited to <0.5 mL of podophyllin or an area of <10 cm^2 of warts per session. No open lesions or wounds should exist in the area to which treatment is administered. Some specialists suggest through washing 1 to 4 hours after application to reduce local irritation.
or
Trichloroacetic acid (TCA) or **Bichloroacetic acid** (BCA) 80 to 90 percent. A small amount should be applied only to the warts and allowed to dry, at which time a white "frosting" develops. This treatment can be repeated weekly if necessary. If an excess amount of acid is applied, the treated area should be powdered with talc, sodium bicarbonate (i.e., baking soda), or liquid soap preparations to remove unreacted acid.
or
Surgical removal either by tangential scissor excision, tangential shave excision, curettage, or electrosurgery.
Alternative regimens:
Intralesional interferon
or
Laser surgery

From Centers for Disease Control and Prevention, 2006, with permission.

Of therapy choices, no data suggest the superiority of one treatment. Thus in general, treatment should be selected based on clinical circumstances and patient and provider preferences.

Molluscum Contagiosum

The molluscum contagiosum virus is a DNA virus that is transmitted by intimate contact. The host response to viral invasion is papular with central umbilication, giving a characteristic appearance (Fig. 3-18). It may be single or multiple and is commonly seen on the vulva, vagina, thighs, and/or buttocks.

FIGURE 3-18

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photograph of molluscum contagiosum. Flesh-colored, dome-shaped papules with central umbilication are noted. *(From Wolff, 2005a, with permission.)*

These lesions are typically diagnosed by visual inspection alone. However, material from a lesion can be collected on a swab, applied to a slide, and submitted to a laboratory for diagnostic staining with Giemsa, Gram, or Wright stains. Molluscum bodies, large intracytoplasmic structures, are diagnostic.

Most lesions spontaneously regress over 6 to 12 months. If removal is preferred, lesions may be treated by cryotherapy, electrosurgical needle coagulation, or sharp needle-tip curettage of a lesion's umbilicated center. Alternatively, topical application of agents used in the treatment of genital warts may also be applied effectively to treat molluscum contagiosum (see Table 3-21).

PATHOGENS CAUSING PRURITUS

Scabies

ETIOLOGY

Sarcoptes scabiei infect skin and result in an intensely pruritic rash. The mite causing this infection is crab-shaped, and the female digs into the skin and remains there for approximately 30 days, elongating her burrow. Several eggs are laid daily and begin hatching after 3 to 4 days (Fig. 3-19). The baby mites furrow their own burrows, becoming reproductive adults in approximately 10 days. The number of adult mites present on an affected patient averages a dozen, although theoretically there could be hundreds. Mites crawl at a rate of two and a half centimeters per minute, and sexual transmission is the most likely cause of initial infection, although it can be seen in household contacts.

FIGURE 3-19

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photomicrograph of burrow with *Sarcoptes scabiei.* A mite is seen at the end of a burrow **(far right)** with seven eggs and smaller fecal particles. *(From Wolff, 2005b, with permission.)*

DIAGNOSIS

A delayed-type 4 hypersensitivity reaction to the mites, eggs, and feces develops and results in erythematous papules, vesicles, or nodules in association with skin burrows. Secondary infection, however, may develop and hide these burrows. Most common infection sites include the hands, wrist, elbows, groin, and ankles. Itching is the predominant symptom in these areas.

Burrows are thin elevated tracks in the skin measuring 5 to 10 mm in length. Definitive testing requires scraping across the burrow with a scalpel blade and mixing these fragments in immersion oil on a microscope slide. Identification of mites, eggs, egg fragments, or fecal pellets is diagnostic.

TREATMENT

Once diagnosed, 1-percent lindane cream (Kwell) is a commonly used agent. A thin layer should be applied from the neck downward with special attention to pruritic areas and the hands, feet, and genital regions. It is recommended that all family members be treated with the exception of pregnant or lactating women and children younger than 2 years. Treatment is effective within 4 hours. Eight to 12 hours after application, a shower or bath should be taken to remove the medication. Only one application is necessary, and bed linens and recently worn clothing should be washed to prevent reinfection.

For pregnant women and young children, 10-percent crotamiton cream or lotion (Eurax, Bristol-Myers Squibb, Princeton, NJ) is recommended since it is nontoxic. It should be applied nightly for two nights, and a bath or shower should not be taken for 48 hours. Another treatment regimen is with a 5-percent permethrin cream (Elimite), which is effective after a single application. It should be washed off in 8 to 12 hours and is safe in children older than 2 months and in pregnant women.

An antihistamine will help reduce pruritus, which can also be treated with a hydrocortisone-containing cream in adults or with emollients or lubricating agents in infants. If these lesions become infected, antibiotic therapy may be necessary.

Pediculosis

ETIOLOGY

Lice are small ectoparasites that measure approximately one millimeter in length (Fig. 3-20). Three species infest humans and include the body louse (*Pediculus humanus*), the crab louse (*Phthirus pubis*), and the head louse (*Pediculus humanus capitis*). Lice attach to the base of human hair with claws, and it is this claw's diameter that determines the infestation site. For this reason, the crab louse is found on pubic hair and other hair of similar diameter, such as axillary and facial hair, including eyelashes and eyebrows.

FIGURE 3-20

A

B

Phthirus pubis. **A.** Pubic lice are seen attached to hair. In addition, nits are seen as dark dots adhered to pubic hair. *(From Long, 1990, with permission.)* **B.** Photomicrograph of *Phthirus pubis.* Claw-like legs are ideally suited for clinging to hair shafts. *(From Birnbaum, 2002, with permission.)*

Lice depend on frequent human blood meals, and pubic lice may travel up to 10 centimeters in search of darkness and a new attachment site for blood. They leave voluntarily if the victim becomes febrile, dies, or if there is close contact with another human. Accordingly, pubic lice usually are sexually transmitted, whereas head and body lice may be transmitted by sharing personal objects such as combs, brushes, and clothing.

SYMPTOMS AND DIAGNOSIS

The main symptom from louse attachment and biting is pruritus. Scratching results in erythema and inflammation, which increases blood supply to the area. Patients may develop pyoderma and fever if secondarily infected. As is true for mites, the number of lice populating a patient averages a dozen.

Each female adult pubic louse lays approximately four eggs a day, which are glued to the base of hairs. Incubation is about 1 month. Their attached eggs, termed *nits,* can be seen attached to the hair shaft away from the skin line as hair growth progresses (see Fig. 3-20). These nits usually require a magnifying glass for identification. Moreover, suspicious flecks on pubic hair or flecks in clothing can be examined microscopically to see the characteristic louse. Other family members should be evaluated, as should sexual contacts.

TREATMENT

Pediculicides kill not only adult lice, but also the eggs. A single application is usually effective, but a second application is recommended within 7 to 10 days to kill new hatches. Nonprescription shampoos contain pyrethrins and piperonyl butoxide and should remain on the skin for at least 1 hour. These include brand names such as Rid, Lice-enz, R&C, Pronto, and A-200 shampoos.

Alternatively, 1-percent lindane shampoo may also be recommended only for pubic lice treatment. Creams and lotions are reserved for scabies. The treatment is applied to the pubic region for 4 minutes and then rinsed. This compound is percutaneously absorbed through excoriated skin, and seizures have been reported if applied too frequently or not washed off.

Eyelash and eyebrow treatment is problematic. These areas are best treated by applying petrolatum (Vaseline, Unilever, Englewood Cliffs, NJ) with a cotton swab at night and washing it off in the morning. Underclothing, bedding, and other infested clothing should be washed and sprayed with Lysol disinfectant (Reckitt Benckiser, Parsippany, NJ). Water temperature greater than 125Â°F is required to kill lice.

In spite of treatment, pruritus may continue and may be relieved by oral antihistamines, anti-inflammatory cream or ointment, or both. The patient should be re-evaluated after 1 week to document louse eradication. The sexually transmitted nature of this disease should be discussed and patients offered testing for other sexually transmitted infections.

URINARY TRACT INFECTIONS

Symptomatic acute bacterial urinary tract infections (UTIs) are among the most common bacterial infections treated by clinicians. It is estimated that there are more than 8 million office visits per year for these infections in the United States. Cystitis accounts for most of these, whereas more than 100,000 patients are admitted to a hospital annually for acute pyelonephritis treatment. Due to the high incidence of UTI, the Infectious Diseases Society of America has developed guidelines for its treatment (Warren, 1999).

Pathogenesis

Because of their pelvic anatomy, women have many more UTIs than men. Bacteria ascending from the colonized urethra enter the bladder and perhaps the kidneys. The short length of the female urethra allows easier access by bacteria to the bladder. Contributing to contamination, the warm moist vulva and rectum are both in close proximity. Similarly, sexual intercourse increases bladder inoculation.

Infections result from the interaction between bacteria and host. Bacterial virulence factors are important, as they enhance colonization and invasion of the lower and upper urinary tract. The principal virulence factors are increased adherence to either vaginal or uroepithelial cells and hemolysin production. The bacterial species most frequently recovered from infected urine culture is *Escherichia coli* (Table 3-22).

Table 3-22 Most Common Etiologic Pathogens in Outpatients with Uncomplicated Acute Cystitis	
Bacterial Pathogen	**Percentage with Pathogen**
Gram-negative	
Escherichia coli	50â€"80
Klebsiella species	6â€"12
Proteus species	4â€"6
Enterobacter species	1â€"6
Morganella species	3â€"4
Gram-positive	
Enterococcus species	2â€"12
Coagulase-negative staphylococci *(S saprophyticus)*	5â€"15
Group B streptococci	2â€"5

Adapted from Fihn, 2003 and Wilson, 2004.

Once within the bladder, bacteria may ascend within the ureters, enhanced by vesicourethral reflux, into the renal pelvis and cause upper tract infection. The renal parenchyma also can be infected by blood-borne organisms, especially during staphylococcal bacteremia. *Mycobacterium tuberculosis* gains access to the kidney through this route and also perhaps by ascension.

Uncomplicated Acute Bacterial Cystitis

DIAGNOSIS

The most frequent presenting complaints in otherwise healthy, immunocompetent nonpregnant women are dysuria, frequency, urgency, and incontinence.

Studies conducted by the National Institutes of Health (NIH), Mayo Clinic, and others have shown that most patients can be treated with a short course of antibiotics without examination, urinalysis, or urine culture for an isolated episode of acute *uncomplicated* bacterial cystitis (Table 3-23). It must be emphasized that a patient in this category can always be seen if she prefers. In addition, women should be instructed on clinical changes that warrant further attention such as fever 100.4Â°C and persistence or recurrence of hematuria, dysuria, and frequency despite treatment.

Table 3-23 Exclusions from 'Uncomplicated' Cystitis
Symptoms of vaginitis (vaginal discharge/vulvar irritation)
Persisting symptoms despite >3 days of treatment of urinary tract infection
Abdominal and/or pelvic pain, nausea, vomiting
Documented temperature above 38Â°C (100.5Â°F)
Recent hospital or nursing home discharge
Documented urologic abnormalities
Recent UTI or urologic surgery
Postmenopausal hematuria
Symptoms >7 days
Immunosuppression
Pregnancy
Diabetes

Women with these exclusions require evaluation to exclude other potential causes of their symptoms. For example, hematuria in a postmenopausal woman may reflect cervical, uterine, or colonic bleeding evident at the time of urination, rather than upper and lower urinary tract infection. Similarly, burning with urination may indicate vulvitis.

Complicated or Recurrent Cystitis

Up to as many as 50 percent of women who suffer an uncomplicated acute bacterial episode of cystitis will have another infection within a year. Up to 5 percent have recurring symptoms soon after treatment. When symptoms develop in such women, the likelihood that a true infection is present is greater than 80 percent.

DIAGNOSIS

Thus, for selected women with complicated or recurrent infections or with persistent or new symptoms during treatment, urinalysis and urine culture are mandatory. For a culture specimen to be informative, it must be accurately collected. A "clean catch" midstream voided urine specimen is usually sufficient. It is mandatory that a patient understands the reasons for and the steps associated with urine specimen collection, which are designed to prevent contamination by other bacteria from the vulva, vagina, and/or rectum. More than one bacterial species identified in a urine culture usually indicates specimen collection contamination.

Initially, a patient spreads her labia and wipes the periurethral area from front to back with an antiseptic tissue. With labia spread, she begins urinating but does not collect the initial stream. A sample is then collected into a sterile specimen cup. The specimen cup is sterile and should be handled by the patient in such a way to avoid contamination. After collection, a urine specimen is delivered promptly to the laboratory and should be plated for culture within 2 hours of collection unless it is refrigerated.

Culture

Urine culture allows accurate identification of an inciting pathogen and susceptibility testing of that pathogen to a variety of antibiotics. Significant bacteriuria is most commonly defined as $\geq 10^5$ bacteria (colony-forming units [cfu]) per milliliter of urine. If urine is collected by either suprapubic aspirate or catheterization, colony counts $\geq 10^2$ cfu/mL are diagnostic. Although a bacterial species may be identified preliminarily, a final urine culture report usually is not available for 48 hours. Thus, empiric treatment is

initially begun but modified, as needed, after culture results are available.

Although anaerobic bacteria are part of the vaginal, colonic, and skin flora, they rarely cause UTIs. Hence, urine culture reports do not note anaerobes except in rare instances in which the laboratory should be alerted to and specifically requested to look for an anaerobic species. Fungi can be identified on routine bacteria media and are reported, but are rare causes of acute cystitis.

Culture is the gold standard for identifying the cause of a urinary tract infection, but no laboratory culture techniques help rapidly identify significant bacteriuria. However, there are rapid tests that give an immediate indication of infection and include microscopy, nitrite testing, and leukocyte esterase testing.

Microscopy

Microscopy of a urine specimen allows identification of both pyuria and bacteria. For identification of leukocytes, a specimen should be examined expeditiously because leukocytes deteriorate quickly in urine that has not been appropriately preserved. Standards to define pyuria are inadequate, other than gross counts. Accordingly, the rapid test for leukocyte esterase has become a surrogate for the microscopic WBC count.

Gram staining is a simple, rapid, and sensitive method for detecting a concentration $\geq 10^5$ cfu/mL of a bacterial species. Rapid identification allows appropriate selection of empiric antimicrobial therapy. However, realistically, such testing is typically limited to patients with complicated urinary tract infections or acute pyelonephritis.

Leukocyte Esterase

This test measures esterase enzyme found in urinary leukocytes and enzyme released from poorly preserved specimens. If used alone diagnostically, this test is most beneficial for its high negative predictive value, especially with bacterial colony counts $\geq 10^5$ cfu/mL. If one combines nitrite and leukocyte esterase testing of a clean-catch uncontaminated voided specimen, the specificity of positive tests approaches 100 percent with uropathogen colony counts of $\geq 10^5$ cfu/mL. The negative predictive value is comparable.

However, if these specimens have been contaminated with vaginal or colonic bacteria, this test can be falsely positive in the absence of a uropathogen. *Trichomonas* species also produce esterases. In addition, very concentrated urine or urine with significant proteinuria or glucosuria will decrease the accuracy of this test.

Nitrites

Bacteria metabolically produce nitrites from nitrates. The bacteria in which this is most frequently observed are Enterobacteriaceae, the family of pathogens most commonly responsible for acute UTIs in women. The major drawback of this test is that it does not identify gram-positive pathogens such as staphylococci, streptococci, enterococci, or *Pseudomonas* species. In addition, it ideally requires testing of the *first morning urine specimen,* because more than 4 hours are required for bacteria to convert nitrates to nitrites at levels that are detectable by the test method. As a single test, the specificity of a positive nitrite test is very high with $\geq 10^5$ cfu/mL of a uropathogen. Its negative predictive value is higher than its positive predictive value.

TREATMENT

There have been changes in not only the etiologic pathogens of acute cystitis, but also sensitivities of those pathogens to antibiotic regimens. During the past two decades, there has been an increase in the frequency of infections caused by group B *Streptococcus* and *Klebsiella* species, and a decrease in infections caused by *E coli.* Also in many locations, sensitivity patterns in *E coli* warrant a shift in initial empiric treatment from trimethoprim-sulfamethoxazole to a quinolone for this infection (Table 3-24).

Table 3-24 Treatment of Urinary Tract Infection

Infection Category	**Antimicrobial Regimen**
Uncomplicated cystitis	Orally 3 days
Local *E coli* resistance <20%	Trimethoprim-sulfamethoxazole DS (160/800 mg) twice daily
Local *E coli* resistance ≥20%	Ciprofloxacin 250 mg twice daily

	or
	Norfloxacin 400 mg twice daily
	or
	Levofloxacin 250 mg daily
	or
	Gatifloxacin 400 mg daily
Complicated/recurrent cystitis	Same as above unless culture and sensitivity dictate change
Postcoital	**Orally once**
	Trimethoprim-sulfamethoxazole SS (80/400 mg) 0.5 to 1 tablet
	or
	Ciprofloxacin 250 mg
	or
	Levofloxacin 250 mg
	or
	Gatifloxacin 400 mg
Intermittent (begin with onset of symptoms)	Same as uncomplicated acute cystitis
Mild pyelonephritis	Oral 7 to 14 days
Gram-negative	Ciprofloxacin 500 mg twice daily
	or
	Norfloxacin 400 mg twice daily
	or
	Levofloxacin 250 mg daily
Gram-positive	Amoxicillin/clavulanic acid 875/125 mg twice daily
Severe pyelonephritis	Intravenous until afebrile 24 to 48 hours, then oral to complete 7 to 14 days therapy
Gram-negative	Ciprofloxacin 400 mg twice daily
	or

	Levofloxacin 500 mg daily
	or
	Gatifloxacin 400 mg daily with or without
	Gentamicin 3 to 5 mg/kg/d
	OR
	Cefoxitin 2 g every 8 hours with or without aminoglycoside
	OR
	Cefotaxime 1 to 2 g two to four times daily with or without an aminoglycoside
Gram-positive	Ampicillin 3 g every 6 hours
	or
	Piperacillin/tazobactam 3.375 g every 6 hours
	or
	Ampicillin/sulbactam 3/1.2 g every 6 hours

DS = double strength; SS = single strength

Adopted from Warren 1999, and Fihn, 2003.

If a woman has a sulfa allergy, she can take trimethoprim alone. Treatment courses of any regimen longer than 3 days result in almost twice the number of adverse events, are not more effective, are more costly, and have higher rates of noncompliance. In addition, single-dose therapy has been shown to be less effective than 3-day regimens. Nitrofurantoin regimens are usually 7 days, and are frequently associated with upper GI symptoms.

For significant dysuria, up to 2 days of a bladder analgesic such as over-the-counter phenazopyridine, 200 mg orally up to three times daily, may give significant relief. However, GI upset, yellow-orange strained urine and clothing, and hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency are potential side effects.

Many recurrences develop after intercourse, and low-dose postcoital dosing or continuous 3-day regimens are usually effective at preventing infection recurrence. A women with two or more episodes of cystitis within 6 months or three infections within a year should be referred for urologic evaluation of her urinary tract.

Asymptomatic Bacteriuria

Asymptomatic bacteriuria is defined as isolation of a specified quantitative count of bacteria in an appropriately collected urine specimen obtained from a person without symptoms or signs referable to urinary infection (Rubin, 1992). In healthy nonpregnant women, the prevalence of this condition increases with age. It is associated with sexual activity, and is more common in diabetics. Moreover, one fourth to one half of elderly women in long-term care facilities have bacteriuria, which is seen primarily in those with chronic neurologic illness and functional impairment.

The Infectious Disease Society of America recommends that nonpregnant premenopausal women not be screened for asymptomatic bacteriuria (Nicolle, 2005). In controlled randomized prospective trials, women randomly given a 1-week course of antibiotic or placebo had similar prevalences of bacteria and incidences of symptomatic infection 1 year after therapy. The same is true for diabetic women, in whom there is evidence of harm with treatment of asymptomatic bacteriuria. Additionally, routine screening is

not recommended for older persons living in the community.

Acute Uncomplicated Pyelonephritis

DIAGNOSIS

This infection may be divided into mild (no nausea or vomiting, normal to slightly elevated blood leukocyte count, and normal to low-grade fever) and severe (vomiting, dehydration, evidence of sepsis, high leukocyte count, and fever). Other symptoms may include those of a lower urinary tract infection and varying degrees of back pain and tenderness to percussion over the region of the kidney(s).

TREATMENT

Traditional therapy for this infection has included hospitalization and intravenous antibiotic treatment for up to 2 weeks. However, more recent studies in young healthy women with normal urinary tracts indicate that 7 to 14 days of oral therapy are sufficient for compliant women with mild infection (see Table 3-24) (Warren, 1999). In one study of more than 50 college women with acute uncomplicated pyelonephritis, resistance to trimethoprim-sulfamethoxazole was 30 percent (Hooton, 1997). Accordingly, an oral fluoroquinolone is recommended treatment unless a pathogen is susceptible to trimethoprim-sulfameth- oxazole. At initial diagnosis, clinicians may also administer a parenteral dose prior to starting oral therapy. Alternatively, if a causative organism is gram-positive, then amoxicillin or amoxicillin/clavulanic acid is recommended.

Hospitalization is warranted for women who display clinical indications at initial evaluation or fail to improve with outpatient therapy.

PELVIC INFLAMMATORY DISEASE

Pelvic inflammatory disease (PID) is an infection of the upper reproductive tract organs. Another diagnosis given to this disease is acute salpingitis. Although all may be involved, the organ of importance, with or without abscess formation, is the fallopian tube. Because of difficulty in accurately diagnosing this infection, its true magnitude is unknown. Many women report that they have been treated for PID when they did not have it, and vice versa.

Microbiology and Pathogenesis

The exact microbiologic pathogens in the fallopian tube cannot be known for any given patient. Studies have shown that transvaginal culture of the endocervix, endometrium, and cul-de-sac contents revealed different organisms from each site in the same patient. In laparoscopic studies, cervical pathogens and those recovered from the fallopian tube or cul-de-sac were not identical. For that reason, treatment protocols are designed so that most potential pathogens are covered by antibiotic regimens.

Classic salpingitis is that associated with and secondary to *N gonorrhoeae* (Table 3-25). Another sexually transmitted disease species frequently recovered from acutely symptomatic women is *T vaginalis.* The lower reproductive tract flora in those patients and in women with bacterial vaginosis are those in which anaerobic species predominate. However, Ness and colleagues (2004) and others have shown that bacterial vaginosis is not a risk factor for development of PID. The sexually transmitted disease species commonly recovered from women diagnosed with PID and reported in Scandinavian studies is *C trachomatis.* It does not, however, cause an acute inflammatory response.

Table 3-25 Pelvic Inflammatory Disease Risk Factors
Douching
Single status
Substance abuse
Multiple sexual partners
Lower socioeconomic status
Recent new sexual partner(s)
Younger age (10 to 19 years)
Other sexually transmitted infections
Sexual partner with urethritis or gonorrhea
Previous diagnosis of pelvic inflammatory disease
Not using mechanical and/or chemical contraceptive barriers
Endocervical testing positive for *N gonorrhoeae* or *C trachomatis*

Upper tract infection is believed to be caused by bacteria from the lower reproductive tract that ascend into the upper tract. It is assumed that ascension of bacteria into the upper tract is enhanced during menstruation due to loss of endocervical barriers. The gonococcus can cause a direct inflammatory response in the human endocervix, endometrium, and fallopian tube and is one of the true pathogens of human fallopian tube epithelial cells. If normal human fallopian tube cells in cell culture are exposed to potential pathogens such as *E coli, Bacteroides fragilis,* or *Enterococcus faecalis,* no inflammatory response results. If the above bacteria are introduced into a fallopian tube cell culture in which gonococci are present and have caused inflammatory damage, an exaggerated inflammatory response results.

In contrast, with intracellular *C trachomatis,* cell-mediated immune mechanisms may be responsible for resulting tissue injury. Little direct permanent damage results from chlamydial tubal involvement (Patton, 1983). Tubal destruction in women with repeated asymptomatic chlamydia may be the result of a delayed hyperimmune response.

Women with pulmonary tuberculosis can develop salpingitis and endometritis. It is assumed that this pathogen is blood-borne, but ascension may still be a possible route. The fallopian tubes also can be infected by direct extension from inflammatory gastrointestinal disease, especially ruptured abscess, i.e., appendiceal or diverticular.

Diagnosis

Pelvic inflammatory disease can be segregated into "silent" PID and PID. Of these, PID can be further subdivided into acute and chronic.

SILENT PELVIC INFLAMMATORY DISEASE

It is presumed that this condition results from multiple or continuous low-grade infection in asymptomatic women. Silent PID is not a clinical diagnosis. Rather, it is an ultimate diagnosis given to women with tubal-factor infertility who lack a history compatible with upper tract infection. Many of these patients have antibodies to *C trachomatis* and/or *N gonorrhoeae.* At laparoscopy or laparotomy, these patients may have evidence of prior tubal infection such as adhesions, but for the most part the fallopian tubes are grossly normal. Internally, however, there are flattened mucosal folds, extensive deciliation, and secretory epithelial cell degeneration (Patton, 1989).

ACUTE PELVIC INFLAMMATORY DISEASE

Criteria for Diagnosis of Acute Disease

In women who are symptomatic, symptoms develop during or following menstruation. The most recent recommended diagnostic criteria presented by the CDC (2006) are for sexually active women at risk for STDs who have pelvic or lower abdominal pain and other etiologies are not feasible. Their diagnosis should be PID if they have uterine tenderness, adnexal tenderness, or cervical motion tenderness. One or more of the following enhances diagnostic specificity: (1) oral temperature >38.3Â°C (101.6Â°F), (2) mucopurulent cervical or vaginal discharge, (3) abundant WBCs on saline microscopy of cervical secretions, (4) elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), and (5) presence of cervical *N gonorrhoeae* or *C trachomatis.*

Symptoms and Physical Findings

Presenting symptoms may include lower abdominal and/or pelvic pain, yellow vaginal discharge, menorrhagia, fever, chills, anorexia, nausea, vomiting, diarrhea, dysmenorrhea, and dyspareunia. Patients also may have infective urinary symptoms. Unfortunately, there is no single symptom or symptom associated with a physical finding that is specific for this diagnosis. Accordingly, other possible sources of acute pelvic pain should be considered (see Table 11-1).

In women with acute PID, leukorrhea or mucopurulent endocervicitis is common and is diagnosed microscopically. In women suspected of having acute PID, endocervical testing for both *N gonorrhoeae* and *C trachomatis* should be performed.

During bimanual pelvic examination, women with acute pelvic inflammatory disease will usually have pelvic organ tenderness. Cervical motion tenderness (CMT) is typically elicited by quickly displacing the cervix laterally with examining vaginal fingers. If a woman has pelvic peritonitis secondary to bacteria and purulent debris that has exuded from the fallopian tubes, this rapid peritoneal movement usually causes a marked pain response. Tapping the cul-de-sac with examining finger(s) will give the examiner similar information. This maneuver usually causes a patient significantly less pain because less inflamed peritoneum is involved.

Abdominal peritonitis may be identified by deep probing and quick release of a hand placed on the abdomen. Alternatively, an examining hand may be positioned with a palm against a woman's mid-abdomen and gently and quickly moved back and forth (shake). This will identify abdominal peritonitis, often with less patient discomfort. In women with PID and peritonitis, usually only the lower abdomen is involved. If all quadrants are involved, suspicion of a ruptured tubo-ovarian abscess should be heightened.

Laparoscopy

In Scandinavian countries, women suspected of having acute PID undergo laparoscopy for diagnosis. Tubal serosal hyperemia, tubal wall edema, and purulent exudate issuing from the fimbriated ends of the fallopian tubes and pooling in the cul-de-sac confirm this diagnosis.

Because of this routine practice, Hadgu and co-workers (1986) assembled criteria that preoperatively clinically predicted acute pelvic inflammatory disease and assessed their validity by the absence or presence of disease at laparoscopy. Criteria included: (1) single status, (2) adnexal mass, (3) age younger than 25 years, (4) temperature >38Â°C, (5) cervical *N gonorrhoeae,* (6) purulent vaginal discharge, and (7) ESR ≥15 mm/hr. The preoperative clinical diagnosis of PID was 97-percent accurate if a woman met all seven criteria. Accordingly, due to the cost of laparoscopy, antimicrobial therapy based on a clinical diagnosis in patients with historical and physical findings suggestive of acute PID is prudent.

Sonography

In women with marked abdominal pain and tenderness, appreciation of upper reproductive tract organs during bimanual examination may be limited. In these patients, vaginal sonography may be used to identify tubo-ovarian abscess or exclude other pathology as the pain source (Figs. 2-15 and 2-16) (Molander, 2001). If sonography does not lead to a clear diagnosis, computed-tomography (CT) scanning may be indicated (Sam, 2002).

Endometrial Biopsy

In women suspected of acute PID, some recommend endometrial biopsy to diagnose endometritis. Polymorphonuclear leukocytes

on the endometrial surface correlate with acute endometritis, whereas plasma cells in the endometrium are found with chronic endometritis. However, women with uterine leiomyomas or endometrial polyps and no PID frequently also have plasma cells present in the endometrium at endometrial biopsy, as do essentially all women in the lower uterine segment. This, in the opinion of many, indicates that in women with mucopurulent secretions, an endometrial biopsy would not provide useful information to alter the diagnosis or therapy (Achilles, 2005).

CHRONIC PELVIC INFLAMMATORY DISEASE

This diagnosis is given to women who describe a history of acute PID and who have pelvic pain. Accuracy of this diagnosis clinically is orders of magnitude less than for acute PID. A hydrosalpinx might qualify as a criterion for this diagnosis (Figs. 9â€“17 and 9â€“18). Realistically, however, it is a histologic diagnosis (chronic inflammation) made by a pathologist. Thus, the clinical utility of this diagnosis is limited.

Treatment

The most beneficial patient outcomes follow early diagnosis and prompt, appropriate therapy. The primary goal of therapy is to eradicate bacteria, relieve symptoms, and prevent sequelae. Tubal damage or occlusion resulting from infection may lead to infertility. Rates following one episode approximate 15 percent; two episodes, 35 percent; and three or more episodes, 75 percent (Westrom, 1975). Also, ectopic pregnancy risk is increased six- to 10-fold and may reach a 10-percent risk for those who conceive. Other sequelae include chronic pelvic pain (15 to 20 percent), recurrent infection (20 to 25 percent), and abscess formation (5 to 15 percent). Unfortunately, women with mild symptoms may remain at home for days or weeks prior to presentation for diagnosis and therapy.

Exactly where a patient should be treated remains controversial. There are proposed criteria that predict better outcome for certain patients with in-hospital parenteral antimicrobial therapy (Table 3-26). However, the high cost of in-hospital treatment prevents routine hospitalization for all women given this diagnosis.

Table 3-26 Recommended Hospitalization Indications for Treatment of Pelvic Inflammatory Disease
Adolescents
Drug addicts
Severe disease
Suspected abscess
Uncertain diagnosis
Generalized peritonitis
Temperature >38.3Â° C
Failed outpatient therapy
Recent intrauterine instrumentation
White blood cell count >15,000/mm^3
Nausea/vomiting precluding oral therapy

ORAL TREATMENT

In women with a mild to moderate clinical presentation, outpatient treatment and inpatient therapy yield similar results. Clinical treatment with oral therapy is also appropriate for women with HIV infection and PID. These women have the same species recovered compared with non-HIV infected patients and response to therapy is similar.

However, if women have more than moderate disease, they require hospitalization. Dunbar-Jacob and associates (2004) showed that women treated as outpatients took 70 percent of prescribed doses, and for less than 50 percent of their outpatient treatment

days. If patients are to be treated as outpatients, an initial parenteral dose may be beneficial. If women do not respond to oral therapy within 72 hours, re-evaluation is indicated and parenteral therapy should be initiated either as an inpatient or as an outpatient if home nursing care is available. This assumes that the diagnosis was confirmed at re-evaluation.

Specific treatment recommendations from the CDC are found in Table 3-27. As mentioned earlier (Treatment), if patients have been recently to California, Hawaii, the east coast, or other areas with increased quinolone-resistant strains of *N gonorrhoeae,* quinolones should not be used. Anaerobes are believed by some to play an important role in upper tract infection and should be treated. Although prospective clinical trials have established that quinolones alone have excellent cure rates, anaerobes are not predictably covered. Hence, metronidazole may be added to improve anaerobic coverage. If patients have BV or trichomoniasis, then metronidazole addition is required, although perhaps not for 14 days.

Table 3-27 Recommended Oral Outpatient Treatment of Pelvic Inflammatory Disease
Regimen A
Levofloxacin 500 mg once daily for 14 days
or
Ofloxacin 400 mg once daily for 14 days with or without
Metronidazole 500 mg twice daily for 14 days
Regimen B
Ceftriaxone 250 mg IM once plus
Doxycycline 100 mg orally twice daily for 14 days with or without
Metronidazole as above
or
Cefoxitin 2 g IM with 1 g oral Probenecid once plus
Doxycycline 100 mg as above with or without
Metronidazole as above
or
Ceftizoxime or cefotaxime 1 gram IM
plus
Doxycycline 100 mg as above with or without
Metronidazole as above

IM = intramuscular.

From Centers for Disease Control and Prevention, 2006, with permission.

PARENTERAL TREATMENT

Any woman who has criteria as outlined in Table 3-26 should be hospitalized for parenteral treatment for at least 24 hours.

Following this, if home parenteral treatment is available, this is a reasonable option. Alternatively, if a woman will be appropriately treated by one of the oral regimens in Table 3-27, then she can be discharged on those medications.

Recommendations for parenteral antibiotic treatment of pelvic inflammatory disease are found in Table 3-28. Of these antibiotics, oral and parenteral routes of doxycycline have almost identical bioavailability, but parenteral doxycycline is caustic to veins. Many prospective clinical trials have shown that either of the listed cephalosporins alone, without doxycycline, will bring a clinical cure. For that reason, doxycycline administration could be reserved until the patient can take oral medication. The recommendation is to continue parenteral therapy until 24 hours after the patient clinically improves and the oral doxycycline should continue to complete 14 days of therapy. Alternatively, if the primary reason for providing doxycycline is to eradicate chlamydia, a 1-g oral dose of azithromycin while the patient is in the hospital will also achieve that goal.

Table 3-28 Recommended Parenteral Treatment of Pelvic Inflammatory Disease
Regimen A
Cefotetan 2 g IV every 12 hours
or
Cefoxitin 2 grams IV every 6 hours plus
Doxycycline 100 mg orally or IV every 12 hours
Regimen B
Clindamycin 900 mg IV every 8 hours plus
Gentamicin loading dose 2 mg/kg followed by a maintenance dose of 1.5 mg/kg every 8 hours. Single daily dosing at 5 to 7 mg/kg per day may be substituted.
Alternative Parenteral Regimens
Levofloxacin 500 mg IV once daily with or without
Metronidazole 500 mg IV every 8 hours
or
Ofloxacin 400 mg IV every 12 hours with or without
Metronidazole 500 mg as above
or
Ampicillin/sulbactam 3 g IV every 6 hours plus
Doxycycline 100 mg orally or IV as above

IV = intravenous.

From Centers for Disease Control and Prevention, 2006, with permission.

For women with an abscess, some also administer oral clindamycin (450 mg every 6 hours) or metronidazole (as shown) to complete therapy. Treatment of a patient with an abscess should include parenteral antimicrobial therapy until the patient has been afebrile for at least 24 hours, preferably 48 to 72 hours. Surgery is rarely required. Although older recommendations for abscess

include hysterectomy and adenexectomy, current antibiotics obviate most surgery. If antibiotic treatment fails, then abscess drainage alone typically will suffice. Often this is possible percutaneously by a radiologist with CT guidance and should be considered initially for abscesses larger than 8 cm.

POSTOPERATIVE INFECTION

Clinical Significance and Risks

Operative site infections continue to account for many hospital-acquired infections. Development of a postoperative infection may result in doubling or even tripling of a predicted hospital stay, resulting in significant patient morbidity and increased health care costs. Risks for postoperative infection are varied and include patient and surgical factors (Table 3-29). Of these, the degree of wound contamination at the time of surgery plays an important role in these infections.

Table 3-29 Risk Factors for Postoperative Surgical Site Infections
Excessive blood loss
Preoperative anemia
Lower socioeconomic status
Immunocompromised patient
Recent operative site surgery
Obesity (abdominal hysterectomy)
Younger age (vaginal hysterectomy)
Older age (abdominal hysterectomy)
Prolonged surgical procedure (>3.5 hours)
Foreign body placement (catheter, drain, etc.)

Because most gynecologic surgical procedures are elective, a gynecologist has time to decrease microbial inoculum. Thus, BV, trichomonal vaginitis, cervicitis, and active urinary tract or respiratory infection ideally are treated prior to surgery.

Wound Classification

Since 1964, surgical wounds have been classified according to the degree of bacterial contamination of the operative site at the time of surgery. As the number of operative site bacteria (inoculum) increases, so too does the postoperative infection rate.

CLEAN WOUNDS

Surgeries that are elective; that are performed for nontraumatic surgical indications; are without operative site inflammation; and avoid the respiratory, alimentary, and genitourinary tracts are included in this category. No break occurs in surgical technique. Thus, most laparoscopic and adnexal surgeries are considered to be in this category, and strictly speaking, supracervical hysterectomy could also be added. Without prophylaxis, infection rates range from 1 to 5 percent. Prophylactic antimicrobial administration *does not* decrease infection rates following these procedures and should not be administered.

CLEAN CONTAMINATED WOUNDS

These are surgical wounds in which the respiratory, gastrointestinal, genital, or urinary tract is entered under controlled conditions and without unusual bacterial contamination. Criteria further define that there can be no break in surgical technique. Infection rates range from 5 to 15 percent. This group encompasses most gynecologic procedures including total hysterectomy, cervical

conization, and dilatation and curettage (D&C). Of these, hysterectomy is the gynecologic procedure most frequently followed by a surgical site infection. These procedures are usually elective, and only hysterectomy requires antimicrobial prophylaxis to reduce postoperative infection rates.

CONTAMINATED WOUNDS

Classic cases in this category include open, fresh, accidental wounds; operations with major breaks in sterile technique or gross GI spillage; and incisions in which acute, nonpurulent inflammation is encountered (Mangram, 1999). Infection rates approximate 10 to 25 percent. For this reason, a minimum of 24 hours of perioperative antimicrobial administration is required, and delayed wound closure may be selected. Laparoscopy or laparotomy for acute salpingitis should be included in this category.

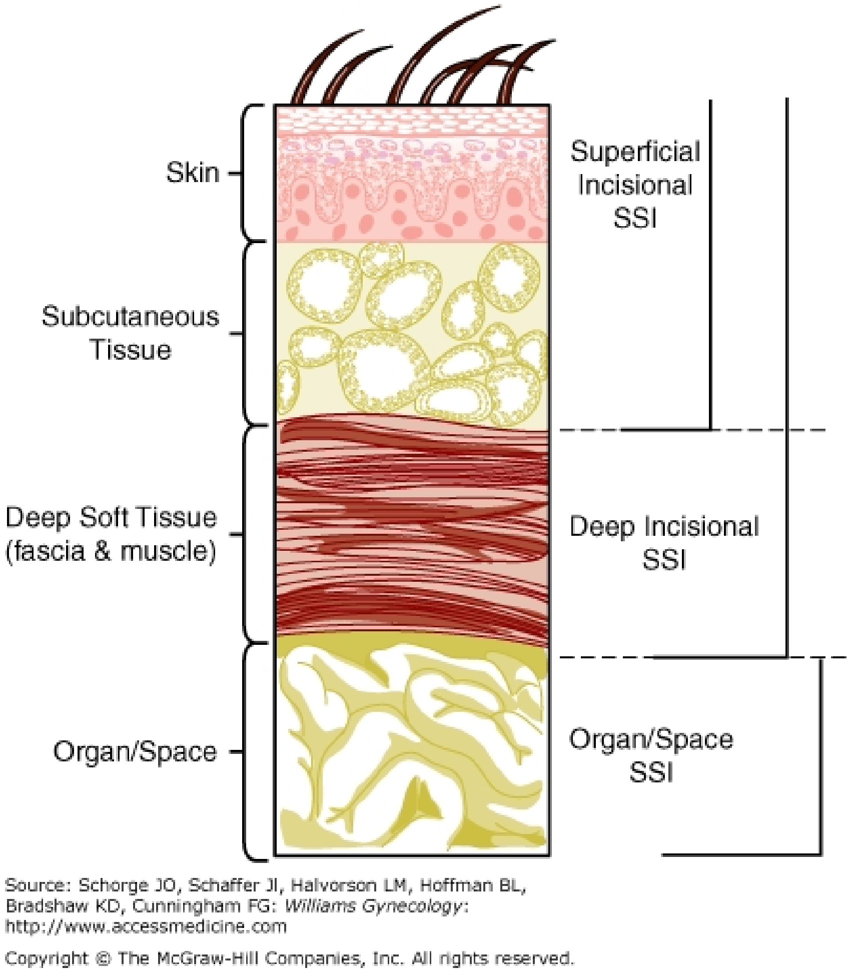
DIRTY WOUNDS

These are typically old traumatic wounds or those that involve existing clinical infection or perforated viscera. These operative sites are clinically infected at the time of surgery, and infection rates range from 30 to 100 percent. Accordingly, therapeutic antimicrobial therapy is required.

Surgical Site Infection Classification

In 1992, the CDC provided definitions of hospital-acquired surgical site infections (SSIs). These were modified by Horan and others during the same year. The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) currently is emphasizing this morbidity during their hospital accreditation process. Thus, hospitals are more attentive to infection rates and to the rates of individual surgeons. In classifying SSIs, there are two categories, incisional and organ space (Fig. 3-21). The incisional group is further subdivided into superficial and deep classes. Criteria for each category are detailed in Table 3-30.

FIGURE 3-21



Anatomy and classification of surgical site infections (SSI). *(Redrawn from Mangram, 1999.)*

Table 3-30 Criteria for Defining Surgical Site Infections
Superficial incisional
Involves only superficial tissues
Develops within 30 days of surgical procedure
Features:
Purulent drainage or bacteria in culture of tissue or fluid
Signs or symptoms
Tenderness or pain
Heat or redness
Localized swelling
Required opening of superficial incision

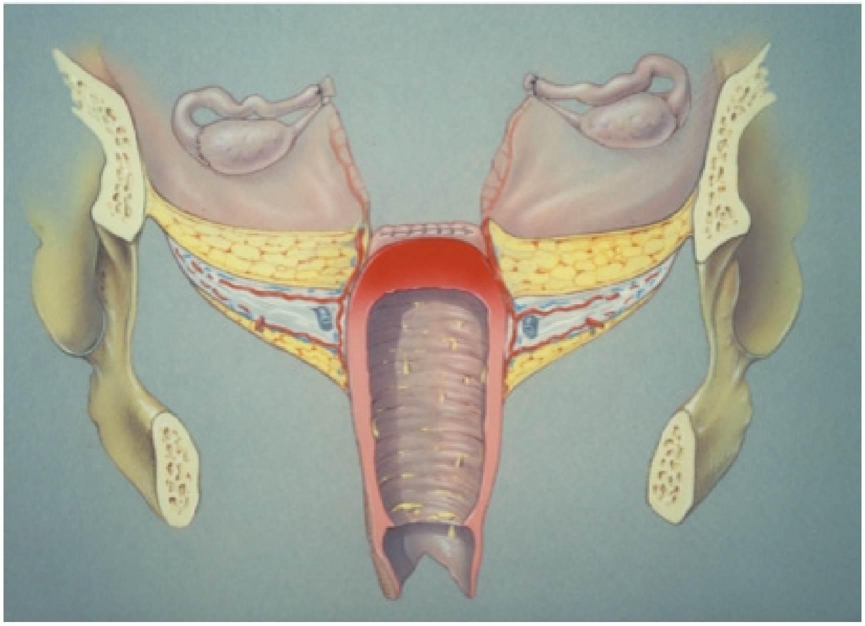
Superficial incision infection diagnosis made by surgeon
Stitch abscesses are not included in this category
Vaginal cuff cellulitis should be included here (see Fig. 3-22)
Deep incisional
Abdominal wall muscle and fascia are involved
Develops within 30 days of surgical procedure
Features:
Purulent drainage from deep incision, not organ or space component, of surgical site
Deep incision that spontaneously dehisces or is deliberately opened by a surgeon in a patient who has at least one of the following signs or symptoms:
Temperature ≥ 38Â°C (100.4Â°F)
Localized pain or tenderness
Abscess or other infection found by reoperation, histopathology, or radiology
Diagnosis made by surgeon
Parametritis (pelvic cellulitis) should be included in this category (see Fig. 3-23)
Organ/space
Develops within 30 days of the surgical procedure
Features:
Purulent drainage from a drain placed through a stab wound into the organ/space
Bacteria recovered from tissue or fluid in that organ/space
Abscess found by reoperation, histopathology, or radiology
Diagnosis made by surgeon

Modified from Mangram, 1999, with permission.

ORGAN/SPACE

These infections develop in spaces or organs other than that opened by the original incision or manipulated during the surgical procedure. Specific sites include the vaginal cuff, urinary tract, and intra-abdominal sites. Of note, vaginal cuff infections are considered in the superficial incisional class and parametritis is classified as a deep incisional infection (Figs. 3-22 and 3-23). In contrast, pelvic infections such as adnexal infection, pelvic abscess, or infected pelvic hematoma fall into the category of organ/space infection (Figs. 3-24 and 3-25).

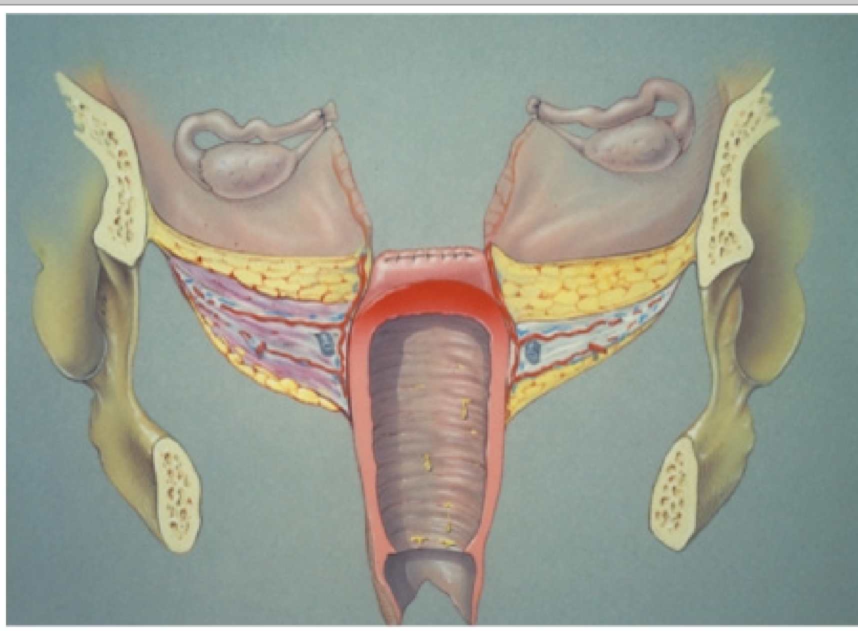
FIGURE 3-22



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Vaginal cuff cellulitis. The vaginal surgical margin is edematous, hyperemic, and tender, and there are purulent secretions in the vagina. Parametria and adnexa are normal during gentle bimanual examination.

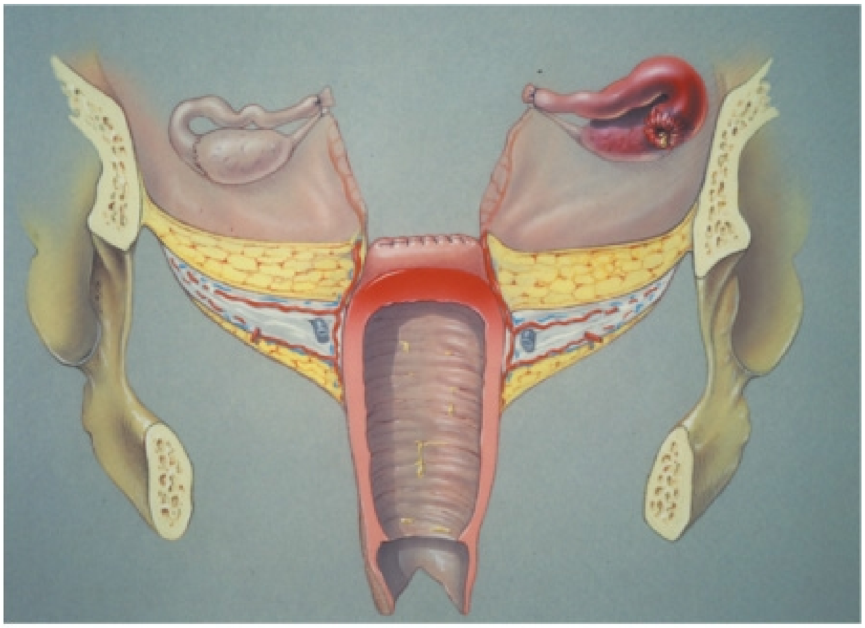
FIGURE 3-23



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Pelvic cellulitis in the right parametrium. It is indurated and tender to palpation; no mass is present.

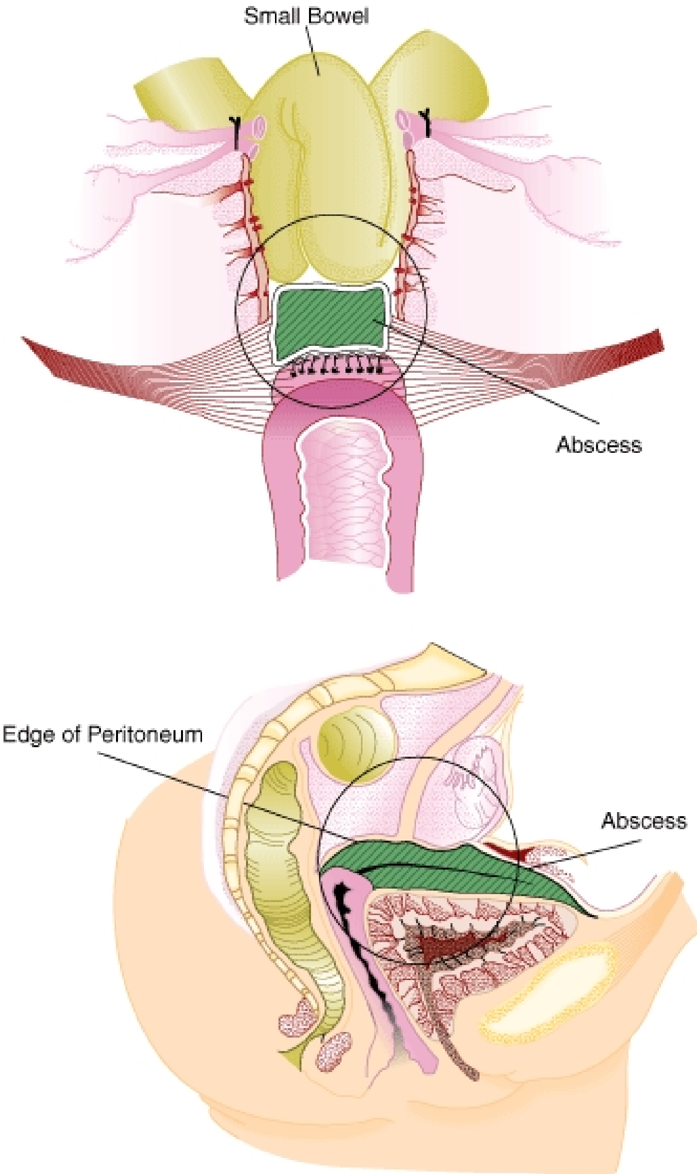
FIGURE 3-24



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Adnexal infection after hysterectomy. The parametria are normal. Tenderness without a mass is appreciated in the adnexal area, and its location is dependent on the surgical procedure.

FIGURE 3-25



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

This is an abscess or infected hematoma that is extraperitoneal and cephalad to the vaginal margins. An adnexal abscess or intraperitoneal abscess should be included, though these are rare.

Diagnosis

FEBRILE MORBIDITY

The most frequently used definition for febrile morbidity is an oral temperature of ≥38Â°C on two or more occasions, 4 or more hours apart, and 24 or more hours following surgery. This condition is seen most frequently after hysterectomy, particularly abdominal hysterectomy; usually is not associated with other symptoms or signs of infection; and does not require antimicrobial therapy! It has been reported in up to 40 percent of women following abdominal and almost 30 percent of women after vaginal hysterectomy with antimicrobial prophylaxis. It resolves without antibiotic treatment in the absence of other symptoms or signs of infection.

A remote nonsurgical site may also serve as an origin of fever. These may include pulmonary complications, intravenous (IV) site phlebitis, and urinary tract infection. Thus, women who develop recurrent temperature elevation require a thorough history and a careful physical examination by the surgeon, seeking not only surgical, but also nonsurgical causes (see Fig. 39-6).

PAIN

Operative site pain (incisional, lower abdominal, pelvic, and/or lower back) following surgery is normal. Patients who develop an operative site infection report increasing pain in the SSI area, and increasing tenderness is present on physical examination. For most gynecologic patients with pelvic infection, this is deep lower abdominal and/or pelvic pain. The most common infection sites requiring antimicrobial therapy are the parametria and the vaginal surgical margin. Pelvic abscess or infected pelvic hematoma is least common, and pain is central. Pain associated with abdominal incision infection is localized to the incision.

PHYSICAL EXAMINATION

Abdominal palpation is an integral part of SSI diagnosis in gynecology. Avoiding an abdominal incision if present, a surgeon gently and deeply palpates the lower abdomen over the surgical site following hysterectomy and normally elicits patient discomfort. Tenderness does not mean an acute surgical abdomen or infection. In the immediate postoperative period, this tenderness is expected, and decreases quickly. Women who develop pelvic cellulitis or cuff cellulitis will have increasing tenderness at gentle depression of the lower abdominal wall over the infected area. Tenderness may be bilateral, but more commonly is more marked on one side than the other. Peritoneal signs are not present. Cellulitis, whether it involves the parametria, adnexa, or vaginal cuff, is not associated with a mass.

In the absence of increasing lower abdominal pain and tenderness, a bimanual examination is not necessary for asymptomatic temperature elevation. However, with a combination of fever, increasing tenderness, and new-onset pain, gentle bimanual examination is required to accurately identify the infection site and to exclude or diagnose a mass. Speculum examination usually is not required, and findings are similar with or without an existing infection. As is true for routine pelvic examination, most information at bimanual examination is obtained from the vaginal fingers.

If a patient is too tender to allow adequate examination, vaginal sonography is indicated. Bowel function is usually not altered by soft tissue cellulitis, but may be by pelvic abscess or infected pelvic hematoma.

CULTURE

Pelvic infections following hysterectomy are polymicrobial, and for that reason, it is difficult to identify true pathogens. Research has demonstrated that bacteria recovered transvaginally from the pelvis of infected and clinically uninfected women are similar. Accordingly, routine transvaginal culturing of women with cuff or pelvic cellulitis does not add useful information. Moreover, a surgeon should not wait for culture results before starting empiric broad-spectrum antibiotic therapy. However, if initial therapy is partially effective or unsuccessful, then a culture will more predictably identify pathogen(s) since therapy will have eradicated other species. The antibiotic regimen should be changed, and culture results may direct this change.

In contrast, abscess or infected hematoma fluid should be cultured since those species are less likely to be vaginal contaminants. The same is true for any fluid or purulent material present in an abdominal incision.

Specific Infections

VAGINAL CUFF CELLULITIS

Essentially all women develop this infection at the vaginal surgical margin after hysterectomy. Normal response to healing is characterized by small-vessel engorgement, which results in erythema and heat. There is vascular stasis with endothelial leakage resulting in interstitial edema, which causes induration. This area is tender, microscopic evaluation of a wet prep reveals numerous WBCs, and purulent discharge is seen in the vagina. This process usually subsides and does not require treatment.

The few women who do require treatment are usually those who present after hospital discharge with mild, but increasing, new-onset lower abdominal pain and have a yellowish vaginal discharge. Findings are as above, but the vaginal cuff is more tender than anticipated at this interval from the initial surgical procedure. Oral antimicrobial therapy with a single broad-spectrum agent is appropriate (Table 3-31). A patient should be re-evaluated in several days to assess therapeutic efficacy. This may be completed by

phone or with an examination if necessary.

Table 3-31 Empiric Antimicrobial Regimens for Post-Gynecologic Surgery Infections

Regimen	Dose
Single-agent intravenous	
Cephalosporin	
Cefoxitin	2 g every 6 hours
Cefotetan	2 g every 12 hours
Cefotaxime	1 to 2 g every 8 hours
Penicillin with or without β-lactamase inhibitor	
Piperacillin	4 g every 6 hours
Piperacillin/tazobactam	3.375 g every 6 hours
Ampicillin/sulbactam	3 g every 6 hours
Ticarcillin/clavulanate	3.1 g every 4 to 6 hours
Carbapenems	
Imipenem/cilastatin	500 mg every 8 hours
Meropenem	500 mg every 8 hours
Ertapenem	1 g once daily
Combination agent intravenous	
Metronidazole	Loading dose 15 mg/kg; maintenance dose 7.5 mg/kg every 6 hours
Ampicillin	2 g every 6 hours
Gentamicin	3 to 5 mg/kg once daily
Clindamycin	900 mg every 8 hours
Gentamicin	As above
with or without Ampicillin	As above
Oral agents	
Amoxicillin/clavulanate	875 mg twice daily
Levofloxacin	500 mg once daily
Clindamycin	300 mg every 6 hours

Metronidazole	500 mg every 6 hours

PELVIC CELLULITIS

This is the most common infection following either vaginal or abdominal hysterectomy. It develops when host humoral and cellular defense mechanisms, combined with preoperative antibiotic prophylaxis, cannot overcome the bacterial inoculum and inflammatory process at the vaginal surgical margin. The inflammatory process spreads into the parametrial region(s) resulting in lower abdominal pain, regional tenderness, and temperature elevation. This usually happens during the late second or third postoperative day. There are no peritoneal signs, and bowel and urinary function are normal. There may be anorexia.

Since patients are discharged on perhaps their first or second postoperative day following vaginal hysterectomy, these patients may be at home before onset of their symptoms, requiring a return visit for evaluation and diagnosis. Hospitalization and treatment with an intravenous broad-spectrum antibiotic regimen is indicated until a patient has been afebrile for 24 to 48 hours, at which time she may be discharged home (see Table 3-31).

Most patients requiring hospitalization for intravenous antibiotic therapy are discharged with an oral antimicrobial prescription. Single-agent therapeutic regimens have been shown in prospective randomized trials to be as effective as combination-agent regimens. These infections are polymicrobial, and the regimen selected must have coverage for gram-positive and gram-negative aerobic and anaerobic bacteria.

ADNEXAL INFECTION

This infection is uncommon and presents almost exactly as does pelvic cellulitis. The difference is in the location of tenderness during bimanual pelvic examination. The cuff and parametrial areas are not usually tender, but the adnexa are areas of tenderness. This infection also may develop after tubal ligation, surgical therapy for ectopic pregnancy, or other adnexal surgery. Empiric antibiotic regimens are identical to those for pelvic cellulitis (see Table 3-31).

OVARIAN ABSCESS/INFECTED PELVIC HEMATOMA

A rare but life-threatening complication following primarily vaginal hysterectomy is ovarian abscess. Presumably, with this infection, surgery is performed in the late proliferative phase of an ovulatory menstrual cycle, and ovaries are in close proximity to the vaginal surgical margin. As expected, physiologic cuff cellulitis develops normally, but when ovulation occurs, bacteria in the area gain access to the ovulation site and the corpus luteum. The corpus luteum many times becomes hemorrhagic, and the blood in this functional cyst is a perfect medium for bacterial growth.

Patients in whom this develops have essentially a normal postoperative course until about 10 days following surgery. At this time they experience, acute unilateral lower abdominal pain, which then becomes generalized. These symptoms reflect rupture of their abscess or infected hematoma and development of generalized abdominal peritonitis. Sepsis commonly follows, and this is a true gynecologic emergency. Exploratory laparotomy is necessary immediately, with preoperative and continued administration of broad-spectrum antimicrobials, evacuation of the abscess, and removal of the affected ovary and adjacent fallopian tube.

Similarly, women rarely may develop a tubo-ovarian abscess (usually a pyosalpinx) identical to that seen as an end result of an episode of acute pelvic inflammatory disease. This process can be managed medically with intravenous antimicrobials, and surgery is usually not required unless rupture follows. Combination antimicrobial therapy should be continued until a woman has been afebrile for 48 to 72 hours.

PELVIC ABSCESS/INFECTED PELVIC HEMATOMA

Pelvic abscess not involving an adnexal structure is also uncommon. Decades ago, prior to routine administration of antimicrobial prophylaxis, vaginal surgical margins were typically sutured in a fashion to create an *open cuff* . This method eliminated space between the vagina and peritoneum. If not performed, this space allowed collection of up to 200 mL of blood, serum, and/or lymph between the vaginal margin and the peritoneum following hysterectomy. These fluids provide an excellent milieu for the overgrowth of bacteria inoculated into the adjacent tissues during the surgical procedure. As a result, prior to the initiation of antimicrobial prophylaxis, pelvic infection rates following hysterectomy were as high as 60 percent, and up to 10 percent of these infections were

cuff abscesses. However, administration of preoperative prophylactic antibiotics predictability decreases these infection rates following hysterectomy regardless of whether an open or closed cuff is created.

Signs and symptoms of pelvic abscess are more central, and a mass is discernible centrally. Transvaginal sonography can accurately characterize the dimensions of this abscess/infected hematoma. Hospital readmission for therapy is necessary. Combination-agent antimicrobial therapy is indicated. Additionally, opening the vaginal surgical margin, if possible, to allow drainage will aid treatment and accelerate patient response. This can usually be done in a treatment room early, avoiding return to the operating room. If necessary, these can be drained with sonographic transvaginal guidance or in the operating room. These abscesses or infected hematomas usually remain confined to the extraperitoneal space, and a patient does not develop peritonitis. Some patients may develop diarrhea due to the proximity of the rectum, which is usually adjacent to the infected space.

This infection is also one that does not present until after a patient is discharged from the hospital. Combination intravenous antibiotics should be administered until a woman has been afebrile 48 to 72 hours.

ABDOMINAL INCISION INFECTION

The superficial and easily accessible location of this infection aids its diagnosis. Although abdominal incision infection may develop alone or with pelvic infection following abdominal hysterectomy, it develops uncommonly after other gynecologic procedures. Unlike pelvic infection, the incidence of this infection is not altered by antimicrobial prophylaxis. Risk factors include obesity, occlusive drapes, excessive use of electrosurgical coagulation, passive drains, and inflammation in the skin through which the incision was made.

Abdominal incisions are usually the most uncomfortable following gynecologic surgery, but pain decreases daily. Erythema and heat are the first physical signs of this infection, which is usually diagnosed on the fourth or fifth postoperative dayâ€"again after discharge from the hospital. A hematoma or seroma may develop in the abdominal wall incision without infection. If these collections are large, opening of the incision and evacuation to prevent infection in those fluids is warranted. Similarly, pus requires incision opening to ensure an intact fascia, as should be done with seromas or hematomas.

Drainage and local care are usually the basis of successful therapy for abdominal incision infection, hematoma, or seroma. Wet to dry dressings stimulate fibroblastic proliferation and development of healthy granulation tissue. Moistening the dry dressing prior to its removal will ease removal and decrease patient discomfort. Several solutions can be used with mechanical dÃ©bridement of wound margins, if necessary. At this stage secondary closure can be considered. Importantly, wounds should be irrigated with normal saline to remove dÃ©briding solutions, as they are caustic to healing tissues. If there is soft tissue cellulitis adjacent to the incision, antimicrobial therapy is a requirement. Wound vacuum-assisted closure (VAC) devices (Wound VAC, Kinetic Concepts International, San Antonio, TX) are available for more serious or larger wound areas that are slow to respond (see Chap. 39, Negative-Pressure Wound Therapy).

TOXIC SHOCK SYNDROME

This condition, caused by a toxin (TSS toxin-1) produced by *Staphylococcus aureus,* appears about 2 days following surgery or onset of menstruation. Menstrual-associated appearance was initially associated with high-absorbency tampons. The vagina must be colonized by a toxigenic staphylococcal strain, and the patient must lack the specific antibody that can block the super- antigen.

The classic nonmenstrual and menstrual toxic shock syndromes have identical clinical symptoms, physical findings, and laboratory results. Women complain of fever, malaise, and diarrhea. In addition to minimal signs of wound infection, if postoperative, a patient has conjunctival and pharyngeal hyperemia without purulence. The tongue is usually reddened, and there is erythema of the skin on the trunk that is neither painful nor pruritic. Temperatures are usually above 38.8Â°C and orthostatic hypotension or shock may be present. This syndrome results from host cytokines released in response to superantigenic properties of the toxin. The criteria for this diagnosis are presented in Table 3-32.

Table 3-32 Criteria for Diagnosis of Toxic Shock Syndrome
Major criteria
Hypotension
Orthostatic syncope
Systolic BP <90 mm Hg for adults
Diffuse macular erythroderma
Temperature ≥38.8ÂºC
Late skin desquamation, particularly on the hands, palms, and soles of feet (1 to 2 weeks later)
Minor criteria (organ system involvement)
Gastrointestinal: diarrhea or vomiting
Mucous membranes: oral, pharyngeal, conjunctival, and/or vaginal erythema
Muscular: myalgia or creatinine phosphokinase level greater than twice normal
Renal: BUN and creatinine greater than twice normal or >5 WBCs/HPF in urine, without concurrent UTI
Hematologic: platelet count <100,000 per mm^3
Hepatic: SGOT, SGPT, and/or bilirubin levels greater than twice normal
Central nervous system: altered consciousness or disorientation without focal localizing signs

BP = blood pressure; BUN = blood urea nitrogen; HPF = high-powered field; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; UTI = urinary tract infection; WBC = white blood cell.

The wound, if present, should be treated as any other wound. It should be cultured to confirm the presence of *S aureus.* However, other cultures (e.g., blood, throat, and cerebrospinal fluid) will be negative. To meet the strict criteria of the diagnosis, a woman must have all major and at least three minor criteria. If this is suspected early and therapy is initiated, the complete syndrome may not develop.

Although it is important to treat with a specific antistaphylococcal antibiotic, the hallmark of therapy is entire system support with large volumes of intravenous fluids and electrolytes to replace massive body fluid losses from diarrhea, capillary leakage, and insensible loss. These patients may develop significant edema and are best managed in an intensive care unit. Even with appropriate management, the death rate has been reported to be as high as 5 percent because of subsequent acute respiratory distress syndrome (ARDS), disseminated intravascular coagulopathy (DIC), or hypotension unresponsive to therapy with resultant myocardial failure. This syndrome may also follow gynecologic surgical procedures such as D&C, hysterectomy, urethral suspension, and tubal ligation.

Serologies for Rocky Mountain spotted fever, measles, and leptospirosis must be negative. Viral infection and group A streptococci can cause a similar presentation.

NECROTIZING FASCIITIS

Although described in the 1870s, it was not named until 1952 by a Parkland Hospital surgeon (Wilson, 1952). It has had various names, including hospital gangrene, acute dermal gangrene, acute streptococcal gangrene, Meleney gangrene, gangrenous

erysipelas, and necrotizing erysipelas. Risk factors for this postoperative incision infection are age over 50, arteriosclerotic heart disease, diabetes mellitus, obesity, debilitating disease, smoking, and previous radiation therapy, all of which are associated with decreased tissue perfusion. Also, it has been reported following tubal sterilization, in a suprapubic catheter site after hysterectomy, in vulvar tissues of diabetics, and even without surgery, especially in vulvar infections of obese diabetic women. Only about 20 percent of cases follow surgery, the majority developing after minor injuries or insect bites. Bacteria recovered from women with this infection are similar to those recovered from any postoperative gynecologic infection site, namely predominantly *E coli, E faecalis, Bacteroides, Peptostreptococcus, S aureus,* groups A and B hemolytic streptococci, and other Enterobacteriaceae.

Although this postoperative superficial incisional infection begins like any other postoperative infection with pain and erythema, the hallmark for its identification is subcutaneous and superficial fascial necrosis, manifested by excessive tissue edema in adjacent areas (Table 3-33). Blisters or bullae form in tissue that has become avascular and is discolored. There is usually a thin gray transudate. Tissue destruction is far more extensive than is evident by surface examination. The skin will slip over underlying tissue, and if incised, due to the lack of vascularity, there will be no bleeding. Severe systemic toxicity may develop. It is beneficial to get radiographs of the infected area prior to treatment to exclude gas in the tissue produced by *Clostridium perfringens* or other clostridial species. The presence of these bacteria is often associated with myonecrosis.

Table 3-33 Criteria for Diagnosis of Necrotizing Fasciitis
Microvascular thrombosis without major vessel occlusion
Extensive necrosis of superficial fascia undermining normal skin
Absence of clostridia in wound and/or blood cultures
No muscle involvement
Intensive WBC infiltrate in necrotic subcutaneous tissue
Moderate-to-severe systemic toxic reaction

WBC = white blood cell.

Although it is important to administer antibiotics, the cornerstone of treatment is prompt recognition with immediate surgical removal of the devitalized tissue down to tissue that bleeds appropriately. This may result in excision of large areas of tissue, leaving significant disfigurement. However, postponing surgery while waiting for antimicrobial activity will only increase the volume of tissue death. Early fatality rates for patients with this infection approached 80 percent according to Stone and Martin (1972).

Wounds are left open and treated as wound infections as described earlier with local hydrotherapy or a wound VAC. Assistance from a general surgeon for potential grafting is often necessary.

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BENIGN DISORDERS OF THE LOWER REPRODUCTIVE TRACT: INTRODUCTION

The lower reproductive tractâ€"comprised by the vulva, vagina, and cervixâ€"harbors a wide spectrum of benign, premalignant, and malignant disease. Lesion characteristics commonly overlap, and differentiating between normal variants, benign disease, and potentially serious lesions can be challenging. However, benign lesions of the lower reproductive tract are common, and in the practice of gynecology, mastery of their identification and treatment is essential.

VULVAR LESIONS

Vulvar skin is more permeable than surrounding tissues because of differences in structure, hydration, occlusion, and susceptibility to friction (Farage, 2004). As a result, pathology involving the vulva is common, although estimates of incidence are difficult because of patient underreporting and clinician misdiagnosis. Lesions may result from infection, trauma, neoplasia, or immune responses. As a result, symptoms vary and may include pain, pruritus, dyspareunia, bleeding, and discharge. Effective therapies are available for most disease, yet embarrassment and fear may prove to be significant roadblocks to care for many women.

Nonneoplasic Vulvar Dermatoses

Classification of nonneoplastic disorders of the vulvar skin and mucosa have undergone multiple iterations over the last 30 years in an attempt to accurately categorize clinical and histologic findings. The International Society for the Study of Vulvovaginal Disease (ISSVD) first convened in 1970 as an international, multidisciplinary society dedicated to the study of vulvar disease. In 1987, the ISSVD adopted nomenclature based on both histopathologic and gross changes (Table 4-1). For those diseases that may display variable histologic appearances, multiple vulvar biopsies may be required for correct classification.

Table 4-1. International Society for the Study of Vulvar Disease Classification of Vulvar Dermatoses
1. Squamous cell hyperplasia
2. Lichen sclerosus
3. Other dermatoses
a. Inflammatory
b. Bullous lesions
c. Ulcerative lesions

From Kiryu, 1990, with permission.

SQUAMOUS CELL HYPERPLASIA (LICHEN SIMPLEX CHRONICUS)

Chronic trauma secondary to rubbing or scratching elicits lichenification, a protective response of the involved skin. Thickening of both the epidermis (acanthosis) and the stratum corneum (hyperkeratosis) produces the characteristic palpable thickening with exaggerated skin margins. Most lesions of squamous cell hyperplasia are symmetric bilaterally and may extend beyond the labia majora.

Behavioral risk factors for developing squamous cell hyperplasia include persistent rubbing, chronic scrubbing, and development of a chronic itch-scratch cycle (Lynch, 2004). There are numerous triggering factors, including chemical substances contained within hygiene products and topical medicines (Virgili, 2003).

Physical examination of affected areas reveals excoriations in a background of erythematous skin. Correlation of these physical findings with historical information is typically sufficient to reach the diagnosis. Treatment involves halting the itch-scratch cycle. Topical steroid ointments help to reduce inflammation, whereas lubricants and sitz baths help to restore the skin's barrier function. If symptoms fail to resolve within 1 to 3 weeks, biopsy is indicated to exclude other pathology.

LICHEN SCLEROSUS

Since the earliest reported cases in the literature in the late 1800s, lichen sclerosus has been plagued with confusing terminology all referring to the same processâ€”lichen sclerosus et atrophicus, lichen albus, Briesky kraurosis vulvae, and balanitis xerotica obliterans. Friedrich (1976) first suggested that the histologic process was more than atrophy. As a result, the ISSVD formally adopted the term *lichen sclerosus* to define this chronic inflammatory skin condition that predominantly affects the anogenital skin (Moyal-Barracco, 2004).

Incidence

Lichen sclerosus classically presents in postmenopausal women, although cases are found in premenopausal women, children, and even men (ages 30 to 50). In a referral dermatologic clinic, lichen sclerosus was found in between 1:300 and 1:1000 cases with a tendency towards Caucasians (Wallace, 1971). Others estimate an incidence of childhood lichen sclerosus to be 1:900 (see Chap. 14, Lichen Sclerosus) (Powell, 2001).

Pathophysiology

Although the cause of lichen sclerosus remains unknown, genetic, infectious, hormonal, and autoimmune etiologies have been suggested. Approximately 20 to 30 percent of patients with lichen sclerosus have other autoimmune processes, in particular thyroid disease and diabetes mellitus (Goolamali, 1974; Meyrick Thomas, 1988). In addition, nearly 75 percent of patients have circulating autoantibodies (Harrington, 1981).

Hormonal differences have been another investigated source. Friedrich and Kalra (1984) compared serum androgen and estrogen levels in women with lichen sclerosus with those in age-matched controls. Both dihydrotestosterone (DHT) and androstenedione levels were significantly lower in women with lichen sclerosus, and a reduced local activity of 5?-reductase was implicated.

Because of this study, 2-percent testosterone ointment was touted to improve lichen sclerosus and lichen sclerosus with squamous cell hyperplasia (Friedrich, 1985; Kaufman, 1974). Unfortunately, these results have not been replicated in subsequent studies and testosterone is no longer recommended in the treatment of lichen sclerosus (Bornstein, 1998; Cattaneo, 1996; Sideri, 1994).

Despite this variety of proposed mechanisms, the cause of lichen sclerosus appears to be multifactoral.

Risks

Despite being classified as a nonneoplastic dermatosis, patients with lichen sclerosus have demonstrated an increased risk of vulvar malignancy. Biopsy-proven cellular atypia typically precedes a diagnosis of invasive squamous cell carcinoma. Thus, women with lichen sclerosus should be examined every 4 to 6 months and new or changing lesions should be biopsied.

Symptoms of Lichen Sclerosus

Despite some women being completely asymptomatic, most women with lichen sclerosus will complain of anogenital symptoms. The hallmark symptom, although nonspecific, is vulvar pruritus and is thought to result from inflammation of local terminal nerve fibers. Pruritus-induced scratching creates a vicious cycle leading to excoriations and further thickening of the vulvar skin. Later symptoms can include dyspareunia due to architectural changes, tenesmus, dysuria, and anorgasmia.

Differential Diagnosis

Although clinical findings may suggest lichen sclerosus, histologic confirmation aids in proper choice of therapy. Lichen planus and vulvar intraepithelial neoplasia (VIN) can both be excluded histologically on biopsy. Although vitiligo produces a depigmented

pattern similar to lichen sclerosus, vulvar architecture remains intact with vitiligo. Estrogen-deficient atrophy will lead to thinning of the epidermis with labial adhesions and associated dyspareunia. In the absence of improvement with local estrogen therapy, a vulvar biopsy will help identify underlying disease. In children, lichen sclerosus poses the need to identify possible prior sexual assault. Sexual abuse and trauma have been suggested as possible provocateurs of lichen sclerosus in genetically predisposed individuals (Ridley, 1993; Weiss, 2002).

Diagnosis

The characteristic clinical picture and histologic confirmation typically lead to the diagnosis. Unfortunately in long-standing cases, histology may be nonspecific, and clinical judgment with close surveillance should guide treatment plans.

Physical Examination

As mentioned earlier, vulvar and perianal involvement is seen in nearly 85 percent of cases. The typical white, atrophic papules may coalesce into porcelain-white plaques and lead to labia minora regression, clitoral concealment, urethral obstruction, and introital stenosis. Over time a lesion may spread to the perineum and anus and form a figure-8 or hourglass shape (Fig. 4-1) (Clark, 1967).

FIGURE 4-1

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Vulvar lichen sclerosus. Note thin and pale vulvar skin and loss of labia minora architecture. *(Courtesy of Dr. William Griffith.)*

Laboratory Testing

A consistent relationship between lichen sclerosus and autoimmune disorders such as Graves disease, type 1 and 2 diabetes mellitus, systemic lupus erythematosus, and achlorhydria, with or without pernicious anemia, have been reported in patients with lichen sclerosus (Bor, 1969; Helm, 1991; Kahana, 1985; Poskitt, 1993). Accordingly, concurrent testing for these disorders is indicated if other suggestive findings are present.

Vulvar Biopsy

Thickened white plaques on the vulva should typically prompt vulvar biopsy to exclude preinvasive and invasive lesions.

To perform the biopsy, the items shown in Fig. 4-2 should be assembled. The biopsy site is first cleaned with an antimicrobial wash and is infiltrated with a 1- or 2-percent lidocaine solution. Biopsy is performed with a Keyes punch biopsy instrument. This tool has an open, circular, sharp-edged tip that is designed to remove a vertical core of tissue when pressed against the skin. Once the dermis has been cut, fine dissecting scissors are used to undermine the circular biopsy and free it.

FIGURE 4-2

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Equipment required for vulvar biopsy. *(Courtesy of Dave Gresham.)*

Keyes punches are available in a variety of diameters, ranging from 2 to 6 mm, and size selection is typically based on lesion dimensions. Following excision, bleeding may be controlled with direct pressure, silver nitrate stick, or Monsel solution.

Treatment

In the absence of curative solutions, the treatment goals for lichen sclerosus include alleviation of symptoms, prevention of progressive anatomic changes, and early detection of malignant transformation. A multidisciplinary approach including patient education, behavior modification, psychological support, and pharmacologic therapy in a dedicated vulvar clinic yield optimal results.

Patient Education

Vulvar hygiene is one of the cornerstones of lichen sclerosus management (Table 4-2). Modifications focus on minimizing both chemical and pressure irritation of the skin.

Table 4-2 Vulvar Hygiene Recommendations
Avoid using gels, scented bath products, moisturizing wipes, and soaps, as they may contain irritants
Use aqueous creams to clean the vulva
Avoid using a harsh washcloth to clean the vulva
Dab the vulva gently to dry
Avoid wearing tight fitting pants
White cotton underwear is preferred
Avoid washing undergarments in commercial washing detergents. Wash and rinse these items separately. Consider using a multirinse process with cold water to remove any remaining detergent
Consider wearing skirts and no underwear when in the house and at night to avoid friction and aid drying

In addition, the chronicity of lichen sclerosus and lack of a cure naturally elicits an array of emotions. International support groups dedicated to lichen sclerosus, such as that found at www.lichensclerosus.org , may offer much needed psychological support.

Topical Corticosteroids

First-line therapy for lichen sclerosus is ultrapotent topical corticosteroid preparations such as 0.05-percent clobetasol propionate (Temovate, GlaxoSmithKline, Philadelphia, PA), or 0.05-percent halobetasol propionate (Ultravate, Bristol-Myers Squibb, New York, NY). Ointment formulations are better tolerated due to their minimally allergenic properties, although some practitioners prefer cream-based products (Table 4-3). Despite theoretical risks of pituitary-adrenal axis suppression and iatrogenic Cushing syndrome if used in large doses for extended periods, clobetasol propionate is believed to have effective anti-inflammatory, anti-pruritic, and vasoconstrictive properties (Paslin, 1996).

Table 4-3 Topical Medication Guide

Steroid Class	Generic Name	Brand Names and(available forms)	Dosage(apply thin layer)
Low potency	Alclometasone dipropionate 0.05%	Aclovate (cream, ointment)	bid or tid
	Betamethasone valerate 0.01%	Valisone (cream, lotion)	qd or bid
	Fluocinolone acetonide 0.01%	Synalar (solution)	bid or tid
	Hydrocortisone base or acetate 1%, 2.5%	Generic versions 1% [OTC] or Hytone, Hycort, or Caldecort 1%, 2.5% (cream, ointment, lotion)	tid or qid
Intermediate potency	Betamethasone valerate 0.1%	Valisone (cream, lotion, ointment)	qd or bid
	Desonide 0.05%	DesOwen (cream, ointment, lotion)	bid or tid
	Fluocinolone acetonide 0.025%	Synalar (cream, ointment)	bid or tid
	Flurandrenolide 0.025%, 0.05%	Cordran (cream, ointment)	bid or tid

	Fluticasone 0.005%, 0.05%	Cutivate 0.005% (ointment),0.05% (cream)	qd or bid
	Hydrocortisone butyrate 0.1%	Locoid (cream, ointment, solution)	bid or tid
	Hydrocortisone valerate 0.2%	Westcort (cream, ointment)	bid or tid
	Prednicarbate 0.1%	Dermatop (cream, ointment)	bid
	Triamcinolone 0.025%, 0.1%	Aristocort, Kenalog (cream, ointment, lotion)	bid
High potency	Amcinonide 0.1%	Cyclocort (cream, ointment, lotion)	bid or tid
	Betamethasone dipropionate 0.05%	Diprolene, Diprosone (cream)	qd or bid
	Desoximetasone 0.05%, 0.25%	Topicort (cream)	bid
	Diflorasone diacetate 0.05%	Psorcon (cream, ointment)	bid to qid
	Fluocinonide 0.05%	Lidex (cream, gel, ointment)	bid or tid
	Fluocinolone acetonide 0.2%	Synalar-HP (cream)	bid or tid
	Halcinonide 0.1%	Halog (cream, ointment, solution)	qd to tid
	Triamcinolone 0.5 %	Aristocort, Kenalog (cream, ointment)	tid or qid
Ultrapotent	Betamethasone dipropionate augmented 0.05%	Diprolene (ointment, gel)	qd or bid
	Clobetasol propionate 0.05%	Temovate (cream, gel, ointment)	bid
	Diflorasone 0.05%	Psorcon (cream, ointment)	bid to qid
	Halobetasol propionate 0.05%	Ultravate (cream, ointment)	bid

bid = twice daily; OTC = over the counter; qd = daily; qid = four times daily; tid = three times daily.

One of the earliest prospective trials by Bracco and colleagues (1993) found 0.05-percent clobetasol propionate superior to both topical 2-percent testosterone and 2-percent progesterone. Subsequent series have supported these findings (Cooper, 2004).

Initiation of treatment is recommended within 2 years of symptom onset to prevent significant scarring. The currently recommended dosing schedule by the British Association of Dermatologists is 0.05-percent clobetasol propionate once nightly for 4 weeks, followed by alternating nights for 4 weeks, and finally tapered to twice weekly for 4 weeks. In affected women, after an initial course of therapy, recommendations for maintenance therapy vary and range from use of corticosteroids only as needed, to ongoing twice-weekly therapy.

Premenarchal vulvar lichen sclerosus has also been shown to respond well to topical clobetasol propionate ointment (see Chap. 14, Lichen Sclerosus) (Smith, 2001). Shorter courses of therapy (2 to 4 weeks) are suggested, and longer courses are reserved for resistant cases.

Intralesional Corticosteroids

One study of eight patients evaluated the efficacy of once-monthly intralesional infiltration of 25 to 30 mg of triamcinolone hexacetonide equally divided bilaterally for a total of 3 months. Severity scores decreased in all categories including symptoms,

gross appearance, and histopathologic findings (Mazdisnian, 1999).

Topical Estrogen

Estrogen therapy is indicated for atrophic changes such as pruritus, epidermal thinning, labial fusion, and dyspareunia. Topical estrogen therapy, however, is not recommended as primary therapy for lichen sclerosus.

Retinoids

Topical tretinoin reduces hyperkeratosis, improves dysplastic changes, stimulates collagen and glycosaminoglycan synthesis, and induces local angiogenesis (Eichner, 1992; Kligman, 1986a, 1986b; Varani, 1989). Virgili and colleagues (1995) evaluated the effects of topical 0.025-percent tretinoin (Retin-A, Ortho Dermatological, Skillman, NJ; Avita, Mylan Pharmaceuticals, Morgantown, WV) applied once daily, five days a week for 1 year. Complete remission of symptoms was seen in more than 75 percent of women. However, more than one-quarter of patients experienced skin irritation, which is common with retinoids (see Chap. 17, Topical Retinoids) (Virgili, 1995).

Tacrolimus

Tacrolimus, (Protopic, Astellas Pharma, Deerfield, IL), a topical calcineurin inhibitor indicated for moderate to severe eczema, has been an agent of recent interest. The drug exerts its action by diminishing antigen-specific T-cell activities and associated proinflammatory cytokine production. Assmann (2003) reported successful treatment of vulvar lichen sclerosus using 0.1-percent tacrolimus twice daily. An advantage of tacrolimus compared with corticosteroids is a theoretical avoidance of atrophic changes since collagen synthesis is unaffected (Assmann, 2003; Kunstfeld, 2003). However, in the face of recent U.S. Food and Drug Administration (FDA) concerns regarding its link to a variety of cancers, clinicians should exercise caution when prescribing such medications for extended use (U.S. Food and Drug Administration, 2006).

Photodynamic Therapy

Investigators have evaluated the effects of phototherapy after pretreatment using 5-aminolevulinic acid in one small series of 12 postmenopausal women with advanced lichen sclerosus. Significant reductions in patient symptoms with continued improvement for up to 9 months were noted (Hillemanns, 1999).

Surgery

Surgical intervention should be reserved for cases of malignancy or significant postinflammatory sequelae. For example, Rouzier and colleagues (2002) described marked improvements in dyspareunia and quality of sexual intercourse if perineoplasty was performed in the face of introital stenosis (Section 41-9, Vestibulectomy). A modified Fenton procedure, which is resection of the posterior fourchette, is an option for patients with scarring at this site. Finally, clitoral adhesions can be surgically dissected to free the hood from the glans. Re-agglutination can be averted using an adhesion barrier such as Surgicel (Ethicon, Piscataway, NJ) in combination with nightly application of ultrapotent topical steroid ointment (Breech, 2000).

Other Dermatoses

INFLAMMATORY

Contact Dermatitis

A primary irritant or an allergic substrate can lead to inflammation of vulvar skin that is termed *contact dermatitis* (Fig. 4-3). This condition is common and in unexplained cases of vulvar pruritus and inflammation, irritant contact dermatitis is diagnosed in as many as 54 percent of patients (Fischer, 1996).

FIGURE 4-3

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Vulvar contact dermatitis. *(From Hewitt, 1991, with permission.)*

Irritant contact dermatitis classically presents as immediate burning and stinging upon exposure to an offending agent. In contrast, patients with *allergic contact dermatitis* experience a delayed onset and an intermittent course of pruritus and localized erythema, edema, and vesicles or bullae (Margesson, 2004). A detailed history will aid in differentiating between the two related yet separate entities. Inquiry regarding new hygiene routines, personal care products, douches, contraceptive methods, topical medications, or perfumes may help identify a new source of alcohols, antiseptics, or surfactants (Table 4-4) (Crone, 2000; Fisher, 1973; Marren, 1992).

Table 4-4 Offending Agents Commonly Implicated in Allergic Contact Dermatitis
Ethylene diamine
Neomycin
Framycetin
Clobetasol propionate
Sodium betabisulfite (found in topical antifungal preparations)
Benzocaine (cross-reacts with sulfa-based drugs)
Lanolin
Thiuram (found in latex condoms)
4-phenylene diamine (found in the dye coloring black underwear)
Cosmetic ingredients
Sanitary pads

Compiled from Crone, 2000, Fisher, 1973, and Marren, 1992, with permission.

With allergic contact dermatitis, patch testing may aid in identifying a responsible allergen(s). Associated conditions, such as candidiasis, psoriasis, squamous cell hyperplasia, seborrheic dermatitis, and squamous cell carcinoma can be excluded through appropriate use of biopsy and cultures.

Treatments for both entities involves removal of the offending agent and/or practice, restoration of the natural protective skin barrier, reduction of inflammation, and avoidance of scratching (Table 4-5) (Farage, 2004; Margesson, 2004).

Table 4-5 Treatment Algorithm for Vulvar Contact Dermatitis
1. Stop offending agents and/or practices
2. Correct vulvar skin barrier function
a. Sitz bath twice daily with plain water
b. Application of plain petrolatum
3. Treat any underlying infection
a. Oral antifungal therapy
b. Oral antibiotic administration
4. Reduce inflammation
a. Topical steroids twice daily for 1 to 3 weeks
i. 0.05% clobatesol propionate ointment
ii. 0.1% triamcinolone ointment
b. Systemic steroids for severe irritation
5. Break the itch-scratch cycle
a. Cool packs (no ice packs, as these may injure skin)
b. Plain, cold yogurt on a sanitary napkin for 5 to 10 minutes
c. Consider an SSRI (sertraline 50 to 100 mg) or an antihistamine (hydroxyzine 25 to 100 mg)

SSRI = selective serotonin-reuptake inhibitors.

Adapted from Margesson, 2004, with permission.

Intertrigo

Friction between moist opposed skin surfaces produces this chronic condition. Although most commonly seen in the inner thigh aspect of the genitocrural folds, skin changes can also be found in the inguinal and intergluteal regions. Secondary bacterial and fungal infections may complicate the disease process.

The initial erythematous phase, if untreated, can progress to intense inflammation with erosions, exudate, fissuring, maceration, and crusting (Mistiaen, 2004). Subsequent hyperpigmentation and verrucous changes may appear. Symptoms typically include burning and itching.

Treatment entails the use of drying agents such as cornstarch and application of mild topical corticosteroids in the face of inflammation. If skin changes do not respond, then seborrheic dermatitis, psoriasis, atopic dermatitis, pemphigus vegetans, or even scabies should be considered. If superinfection with bacteria or yeast develops, appropriate culture-based therapy is warranted.

To prevent recurrent outbreaks, obese patients are encouraged to lose weight if possible. Other preventive recommendations include wearing light, loose clothing made of natural fibers (Janniger, 2005).

Atopic Eczema

Classically presenting in the first 5 years of life, atopic dermatitis presents as a severely pruritic dermatitis that follows a chronic, relapsing course. Scaly patches with fissuring are evident on examination. Atopic eczema affects 10 to 20 percent of children in the United States, and these individuals may later develop allergic rhinitis and asthma (Spergel, 2003).

Topical corticosteroids and less commonly, immunomodulators, such as tacrolimus, can be used to control flares (Leung, 2004). In the presence of dry skin, local hydration using emollients and bath oil can offer relief.

Psoriasis

Approximately 1 to 2 percent of the United States population is affected by psoriasis, a condition characterized by thickened, red areas of skin covered with silvery scales on extensor surfaces (Fig. 4-4).

FIGURE 4-4

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Psoriasis. Raised, inflamed, red plaques are covered with silvery-white scales. *(From Wolff, 2005b, with permission.)*

Over the last decade, insight into T-cellâ€"mediated pathogenesis has revolutionized the understanding of this disease (Chamian, 2004). It is felt that type 1 T-cellâ€"mediated inflammatory reactions in the skin are linked with keratinocyte hyperproliferation (Lebwohl, 2003; Zhou, 2003). This research has formed the conceptual framework for T-cellâ€"targeted biologic immunoregulators. Alefacept (Amevive, Astellas Pharma, Astellas Pharma, Deerfield, IL), efalizumab (Raptiva, Genentech, South San Francisco, CA), and infliximab (Remicade, Centocor, Horsham, PA) are approved by the FDA for treatment of psoriasis (Ritchlin, 2006).

Psoriasis can be exacerbated by nervous stress and menses with remission experienced during summer months and in pregnancy. Pruritus may be minimal or absent, and psoriasis is often diagnosed by skin findings alone.

Several treatments are available for psoriasis, and those recalcitrant to topical corticosteroids are best managed by a

dermatologist. Topical corticosteroids are widely used for their rapid onset of action and effectiveness. Vitamin D analogues such as calcipotriene (Dovonex, Warner Chilcott, Rockaway, NJ), though similar in efficacy to potent corticosteroids, are associated with local irritation, which is seen in more than 20 percent of patients (Smith, 2006). Phototherapy with ultraviolet B light and photochemotherapy (psoralen plus ultraviolet A light, PUVA) offer short-term relief, but long-term treatment plans require a multidisciplinary team approach (Griffiths, 2000). Newer biologic agents such as efalizumab, alefacept, and infliximab, lack data on long-term safety and efficacy (Smith, 2005).

LICHEN PLANUS

Incidence and Etiology

Lichen planus, an uncommon disease that involves both cutaneous and mucosal surfaces, equally affects men and women between age 30 and 60 years (Mann, 1991). Although much is unknown about the etiology of lichen planus, it is believed to be related to T-cellâ€"related autoimmunity to basal keratinocytes (Goldstein, 2005).

Diagnosis

Women typically complain of chronic vaginal discharge with intense pruritus, dyspareunia, and postcoital bleeding. On physical examination, papules classically seen with lichen planus are violaceous, flat-topped, shiny polygons most commonly present on flexor surfaces of the extremities, trunk, or buccal mucosa (Fig. 4-5) (Goldstein, 2005; Zellis, 1996). Additionally, white striae (Wickham striae) are frequently found in conjunction with the papules, and nail dystrophy may be noted.

FIGURE 4-5

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Oral lichen planus. Wickham striae are seen as white reticulated lines that are visible in the lesions of lichen planus. *(Courtesy of Dr. Edward Ellis.)*

Vulvar lichen planus can present as one of three variants: (1) erosive lichen planus, (2) papulosquamous lichen planus, and (3)

hypertrophic lichen planus. Table 4-6 summarizes the most common mimickers of lichen planus. Lichenoid drug-induced lesions have also been implicated (Table 4-7).

Table 4-6 Differential Diagnosis of Lichen Planus

Class of Lichen Planus	Mimicking Condition	Key Features of Mimicking Condition
Erosive lichen planus	Lichen sclerosus	No vaginal involvement; confirmed by histology
	Pemphigoid vulgaris or benign mucous membrane pemphigoid	Shallow erosive ulcerations with rare vaginal involvement; immunofluorescent histology will confirm (Note: biopsy normal adjacent epithelium)
	BehÃ§et disease	No vaginal involvement; will have ocular involvement; inflammation is perivascular
	Plasma cell vulvitis	Rare; no oral lesions
	Erythema multiforme major/Systemic symptoms	Stephen-Johnson syndrome
	Desquamative inflammatory vaginitis	Vaginal discharge will have elevated pH, sheets of white cells, and parabasal cells
Papulosquamous lichen planus	Molluscum contagiosum	Biopsy confirmation
	Genital warts	Biopsy confirmation
Hypertropic lichen planus	Squamous cell carcinoma	Biopsy confirmation

Compiled from Goldstein, 2005, Kaufman, 1974, and Moyal-Barracco, 2004, with permission.

Table 4-7 Drug-Induced Lichen Planus

Sufficient evidence to support causation

- β-blockers
- Methyldopa
- Penicillamine
- Quinidine
- Quinine
- Nonsteroidal anti-inflammatory agents

Insufficient evidence to support causation

- Angiotensin-converting enzyme inhibitors
- Gold
- Lithium
- Carbamazepine

- Sulfonylurea agents

Compiled from Thompson, 1994, with permission.

Women with a genital lesion suspicious for lichen planus require a thorough dermatologic survey to seek extragenital lesions and vice versa (Belfiore, 2007). Nearly one quarter of women with oral lesions will have vulvovaginal involvement, and most with erosive vulvovaginal lichen planus will have oral involvement (Pelisse, 1989).

Treatment of Vulvar Lichen Planus

Of the three lichen planus variants, erosive lichen planus is the most difficult to treat. Pharmacologic therapy remains first-line therapy for this condition. Additional treatment includes improving vulvar hygiene, providing psychological support, and discontinuing medications associated with lichenoid changes.

Cooper and Wojnarowska (2006) prospectively evaluated the clinical course of 114 women with erosive lichen planus treated with ultrapotent topical corticosteroids. Despite more than 70 percent of women exhibiting good response to twice-daily therapy used for 3 months followed by maintenance therapy, only 9 percent achieved complete remission of erosive signs. Alternatively, more than 90 percent of women treated with a preparation containing 0.05-percent clobetasol butyrate, 3 percent oxytetracycline, and 100,000 U/g nystatin were symptom free during initial treatment. Antibiotics are used often used for dermatoses because of their anti-inflammatory and antimicrobial effects.

Other agents shown to be beneficial in small case series include systemic corticosteroids, topical tacrolimus ointment, topical cyclosporine, and oral retinoids (Eisen, 1990; Hersle, 1982; Lozada-Nur, 1997; Morrison, 2002; Pelisse, 1989).

Treatment of Nonvulvar Cutaneous Lichen Planus

Laurberg and co-workers (1991) performed a placebo-controlled trial comparing acitretin, 30 mg orally daily (Soriatane, Connetics, Palo Alto, CA) with placebo in 65 patients and found significant improvement in nearly 65 percent of patients. Acitretin is a retinoid administered daily orally. Alternatively, unpublished experience describes symptom improvement using topical corticosteroids (Cribier, 1998; Oliver, 1993).

Treatment of Vaginal Lichen Planus

Anderson and colleagues (2002) found vaginal corticosteroid suppositories of hydrocortisone 25 mg twice daily with a tapering dose to maintain symptom relief has been shown to offer symptomatic and clinical improvement in more than 75 percent of women. Combining local corticosteroid therapy with vaginal dilators may help restore coital function in patients with moderate vaginal synechiae. Surgical adhesiolysis is a last resort.

Fox-Fordyce Disease

Intensely pruritic, discrete, dome-shaped, papular lesions confined to the apocrine sweat gland openings in reproductive-aged women is known as Fox-Fordyce disease. Keratotic plugs in the upper hair follicles leading to obstruction and rupture is felt to be one of the pathophysiologic features of this disease. The mechanism behind its hormonal and emotional exacerbations remains unclear, but women frequently complain of intense axillary or vulvar pruritus before and during menses and after an emotional event. Topical corticosteroids, antibiotics, ultraviolet phototherapy, topical tretinoin, and even oral contraceptives have been used with variable results (Feldmann, 1992; Giacobetti, 1979; Tkach, 1979).

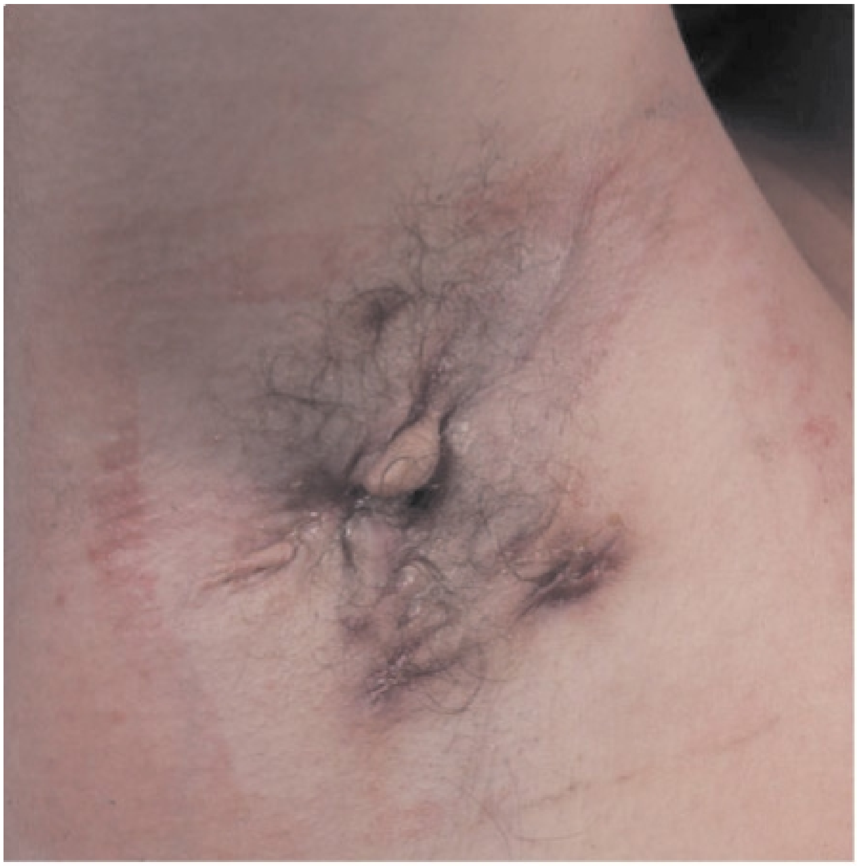
Hidradenitis Suppurativa

Within intertriginous areas, recurrent papular lesions that involve apocrine gland-bearing follicular epithelium typify hidradenitis suppurativa. Little is known about this disease that predominantly affects women (Parks, 1997). Over one quarter of patients will relate a family history of disease, and some authors speculate an autosomal dominant inheritance pattern (der Werth, 2000). Although Mortimer and colleagues (1986) found higher plasma concentrations of androgens in women with hidradenitis suppurativa, others have been unable to verify those findings (Barth, 1996). Bacterial superinfection with *Staphylococcus aureus* and coagulase-negative staphylococci is common but appears to be independent of the actual disease process (Brook, 1999;

Jemec, 1996).

In otherwise healthy women, hidradenitis suppurativa evolves as an insidious discomfort followed by papule or nodule formation (Fig. 4-6). Over time, the process recurs with coalescence of nodules to form large abscesses. Rupture and resolution leads to fibrosis and formation of sinus tracts that drain from cutaneous tissues to the skin surface. Scarring and edema of surrounding structures leads to functional limitations and decreased quality of life (der Werth, 2001; Konety, 1996). Biopsy is typically not required for diagnosis.

FIGURE 4-6



Axillary hidradenitis suppurativa. Scarring and intradermal connecting sinuses are common in more severe forms of this disease. *(From Wolff, 2005a, with permission.)*

Treatment of early phases includes systemic antibiotics, topical antiseptics, and warm compresses to help restore the skin barrier. Since superinfection of hidradenitis suppurativa is polymicrobial, aerobic and anaerobic cultures help guide antibiotic selection. Empiric use of clindamycin in conjunction with a quinolone, however, is reasonable. Sawers and colleagues (1986) found the antiandrogen, cyproterone acetate 50 mg, in conjunction with ethinyl estradiol 50 μg, both orally daily, demonstrated benefit.

Infliximab, a monoclonal TNFa antibody, has had favorable results in case report series (Adams, 2003; Sullivan 2003). The specific relationship between TNFa inhibition and the mechanism by which infliximab exerts its clinical effects is unknown. Its potent anti-inflammatory effects are suspected for its efficacy. However, infliximab has been associated with serious side effects when used to treat rheumatoid arthritis, Crohn disease, and psoriasis. Moreover, in case reports describing its use in patients with hidradenitis suppurativa, infusion reaction, infection, allergic reaction, and neuropathy were cited complications, even during short-term use (Fardet, 2007; Fernandez-Vozmediano, 2007). Accordingly, larger prospective studies are needed.

Surgical excision is reserved for severe cases resistant to medical interventions. Prior to surgical removal of involved tissue, the extent and course of all sinus tracts should clearly be traced. Other surgical options include marsupialization of solitary abscesses or CO_2 laser excision of involved epithelium followed by healing by secondary intention (Finley, 1996). Patients should be reminded that postoperative recurrences do develop, and close surveillance is warranted.

Bullous Lesions

ERYTHEMA MULTIFORME MAJOR (STEVENS-JOHNSON SYNDROME)

Since the initial description by Stevens and Johnson in 1922, confusion continues to exist on the classification of bullous skin lesions with mucosal and cutaneous involvement. Stevens-Johnson syndrome or erythema multiforme major (EMM) is an uncommon condition with a mean age of onset of 25 years (Bagot, 1993; Strom, 1991).

Although patients with the HLA-Bw44 antigen are felt to be more susceptible to developing EMM, timing between drug exposure and clinical patterns provides the best correlation (Mondino, 1982). Antibiotics are the most common cause of EMM, followed by analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), psychoepileptics, and agents used to treat gout.

Patients initially present with a typical target lesion described as having three rings: a bright red inner ring, lighter-pink middle ring, and a darker-pink outer ring. A febrile illness with malaise, headaches, and cough predates the dominant finding of skin detachment (Letko, 2005; Power, 1996). Nearly all patients will exhibit some form of mucosal involvement, ranging from oral and ocular erosions to pulmonary, gastrointestinal, or even renal involvement.

Another condition hypothesized to be a variant of the same disease process is toxic epidermal necrolysis (TEN) (Letko, 2005). This condition develops in an older population (mean age between 45 and 60 years) and carries a much higher mortality rate, quoted to be between 10 and 70 percent (Revuz, 1987). Cutaneous and mucosal defects are similar to those of EMM with the key differences being an absence of the characteristic target lesion, but instead an intense erythema that rapidly progresses to epidermolysis (Heimbach, 1987).

Management of both acute EMM and TEN is primarily removal of the offending drug and supportive care to manage the most commonly seen complications: hypovolemia from increased insensible losses, bronchiolitis obliterans, bloody diarrhea, and increased infections due to loss of the skin barrier (Tsunoda, 1990).

PEMPHIGUS VULGARIS

Blistering of the oral cavity and skin are typical of this rare autoimmune disorder that affects individuals aged 40 to 60 years (Bystryn, 2005). Estimated to affect fewer than 5 cases per million annually, this rare disease if untreated is almost always fatal.

Clinically, pemphigus vulgaris usually begins with painful, nonhealing ulcers of the buccal mucosa, although lesions can be found on the labia, palate, and tongue. Lesions are multiple, irregularly shaped, and superficial (Bystryn, 2005). An immunofluorescent assay for tissue-fixed and circulating intracellular antibodies to keratinocyte surface antigens is the most specific diagnostic test (Nisengard, 1975).

Mortality in untreated cases is high and primarily results from infection and metabolic complications. Initial therapy includes systemic corticosteroids (prednisone orally 60 to 80 mg daily), and the milligram dose is increased until new lesions cease formation and established wounds begin healing. Plasmapheresis and intravenous immunoglobulin (IVIG) have been studied and are considered second-line agents (Harman, 2003). Long-term therapy includes gradual discontinuation of systemic medications and transition to topical corticosteroids to suppress new lesions.

Ulcerative Lesions

APHTHOUS ULCERS

Nearly 25 percent of women in the second and third decade of life will experience these self-limited mucosal lesions. Classically found in nonkeratinized oral mucosa, aphthous ulcers may also develop on vulvovaginal surfaces. Lesions are painful and can recur once every few months.

Although the etiology of aphthous ulcers is unknown, some theorize the origin to be immunologically mediated epithelial cell

damage (Rogers, 1997). Other described triggering factors include trauma, malnutrition, infection, and hormonal fluctuation. In addition, deficiencies in vitamin B_{12}, folate, iron, and zinc have been reported to be causative (Torgerson, 2006). Despite the self-limited nature of this process, lesions that persist for more than 14 days can lead to painful scarring (Rogers, 2003).

Treatment for aphthous ulcers diagnosed at the onset of ulceration can be treated with high-potency topical corticosteroids. Systemic corticosteroids taken orally can help decrease inflammation in cases initially resistant to topical corticosteroids. Finally, colchicine, dapsone, and thalidomide have been shown to be effective.

BEHÃ§ET DISEASE

This is a rare, chronic, multisystem inflammatory process that affects patients in their twenties and thirties. This condition is characterized by mucocutaneous lesions with associated ocular and systemic inflammation.

Although the exact etiology of BehÃ§et disease remains unknown, possession of the HLA-B51 allele carries genetic predisposition in some populations. Infectious triggers have been investigated, although a definitive agent has not been identified. In cases with multiorgan involvement, vasculitis with inflammatory damage explains the pathogenic process.

BehÃ§et disease produces lesions that generally heal within 7 to 10 days without major scarring. Nevertheless, associated pain can be debilitating. The process does have a variable course during pregnancy but no adverse maternal or fetal outcomes have been reported (Marsal, 1997). Treatment for lesions is similar to that of aphthous ulcers.

Lesions of Pigmentation

HYPERPIGMENTATION

Several theories explain the spectrum of hyperpigmentation disordersâ€"genetic predisposition, environmental toxins, sequelae of chronic diseases, and drug reactions (Grimes, 2006).

Acanthosis Nigricans

Velvety, brown, poorly marginated plaques located in the flexures, especially the neck, axillae, and genitocrural folds, characterize acanthosis nigricans.

Acanthosis nigricans is a commonly recognized dermatologic complication of obesity, with an incidence estimated up to 75 percent (Hud, 1992; ÃŽosipovitch, 2007). A significant relationship has also been reported between degrees of obesity and concurrent hyperinsulinemia (see Chap. 17, Acanthosis Nigricans) (Garcia-Hidalgo, 1999).

The mechanism behind acanthosis nigricans formation originates with cellular insulin resistance leading to compensatory hyperinsulinemia. Insulin binds to insulin-like growth factor (IGF) receptors in peripheral tissue leading to proliferation of keratinocytes and dermal fibroblasts (Cruz, 1992; Hermanns-Le, 2004).

Treatment includes correction of hyperinsulinemia. Weight loss can ameliorate insulin resistance leading to a reduction in insulin/IGF receptor complexes and subsequent skin lesion improvement. The vitamin D3 analog calcipotriene inhibits proliferation and increases differentiation of keratinocytes, leading to clearing of acanthosis nigricans (Bohm, 1999).

Melanoma

This is the second most common vulvar malignancy and accounts for up to 10 percent of all vulvar cancers. However, melanomas that develop in the vulva comprise only 1 to 2 percent of all melanoma cancer cases. Presenting symptoms include burning, pain, pruritus, a bleeding mass, local discoloration or ulcerations, and even dysuria (Trimble, 1992). Diagnosis and treatment of these lesions is discussed in Chapter 31, Melanoma (Ragnarsson-Olding, 1999; Wechter, 2004; Weinstock, 1994).

Nevus

Acquired nevi commonly develop in adolescence in sun-exposed areas, although vulvar skin is not immune (Krengel, 2005). In contrast, congenital nevi may be found on any skin surface at any age. Pigmented nevi warrant close surveillance, as more than half of all melanomas arise from pre-existing nevi.

Nevi are classified into three primary groups: junctional, compound, and intradermal. Junctional nevi are less than 1 cm in

diameter, flat with minimal surface elevation, and derive from melanocytes within the epidermis. Their color is uniform and lesion margins are well demarcated. Junctional nevi are the ones most likely to become malignant. Compound nevi involve both the dermis and epidermis. Lesions possess regular margins and range in size from 4 to 10 mm. As these lesions age, they may progress into intradermal nevi, which lie completely within the dermis and can become papular or pedunculated.

Therapy for nevi is primarily conservative with close observation in asymptomatic individuals. As lesions become palpable with subsequent irritation and bleeding, surgical excision serves both a diagnostic and therapeutic role.

DEPIGMENTATION

Vitiligo

The loss of epidermal melanocytes in areas of depigmented skin is termed *vitiligo* (Fig. 4-7). Global prevalence of this disease varies from 0.1 to 0.2 percent, with the incidence peaking in the second decade. No racial, ethnic, or socioeconomic populations harbor a greater propensity towards this disease, although the disease is more disfiguring in members of darker-skinned ethnic groups (Grimes, 2005).

FIGURE 4-7

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Vulvar vitiligo. *(Courtesy of Dr. William Griffith.)*

Genetic factors have emerged as the most common cause of vitiligo (Zhang, 2005). Although its complex inheritance pattern is not fully understood, approximately 20 percent of patients have at least one affected first-degree relative. Vitiligo may also share pathogenesis with other autoimmune disorders, such as Hashimoto thyroiditis, Graves disease, diabetes mellitus, rheumatoid arthritis, and even psoriasis (Boissy, 1997).

Most commonly, depigmentation is generalized and symmetric, although distribution may also be acral, acrofacial, localized, and segmental. Lesions progress slowly over years.

Recently, there have been a number of advances in the treatment of vitiligo, including narrow-band UV-B phototherapy, targeted light therapy, and topical immunomodulators (Grimes, 2005; Yones, 2007).

Dermatologic Manifestations of Systemic Disease

CROHN DISEASE

Transmural granulomatous inflammation affecting the submucosa anywhere along the gastrointestinal tract is characteristic of Crohn disease. Four types of cutaneous involvement are associated with Crohn disease and include: (1) direct extension from the involved bowel; (2) extraintestinal involvement of the vulva, penis, abdominal wall, extremities, and submammary area; (3) pyoderma gangrenosum, erythema nodosum, and erythema multiforme; and (4) nutritional deficiency-related skin lesions (Burgdorf, 1981; Kim, 1992). Seen in nearly a quarter of women with Crohn disease, the classic perineal and vulvar deep, slit-like, "knife cut" ulcers seen in the inguinal, genitocrural, and interlabial folds typify extraintestinal involvement (Donaldson, 1978). Such lesions may predate gastrointestinal symptoms (Patton, 1990).

Therapy that is used to treat gastrointestinal manifestations of Crohn disease should also benefit metastatic Crohn lesions. Extensive genital surgery can be avoided with appropriate vulvar hygiene, proper nutrition, and close collaboration with a gastroenterologist familiar with the latest therapies for Crohn disease. In the event that surgical management is required, excision of the fistulous tracts is attempted, while reserving a total vulvectomy for extensive disease.

Solid Vulvar Tumors

Most solid vulvar tumors are benign and arise from local tissue. Less commonly, malignant lesions arise on the vulva and are typically of squamous cell epithelial origin. Rarely, solid vulvar tumors may develop as metastatic lesions (Fig. 4-8). Accordingly, many growths warrant biopsy if their nature is not obviously determined by visual inspection.

FIGURE 4-8

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Solid vulvar tumor. Biopsy revealed endometrial cancer metastatic to the clitoris. *(Courtesy of Dr. William Griffith.)*

EPIDERMAL

Acrochordon

Commonly known as a skin tag, acrochordons are benign polypoid fibroepithelial lesions. These lesions are most often seen on the sides of the neck, axilla, or groin, and range from 1 to 6 mm in diameter. Of note, recent reports have found a relationship between acrochordons and diabetes mellitus (Demir, 2002). Insulin-mediated fibroblast proliferation may explain this relationship.

Clinically, an acrochordon is a soft sessile or pedunculated mass that is usually skin-colored and devoid of hair. Swelling or ulceration may be noted following chronic irritation or trauma. Surgical removal is recommended in cases of chronic irritation or for cosmetic reasons. Such lesions are easily removed under local anesthesia in an office setting.

Seborrheic Keratosis

Occasionally, vulvar manifestations of seborrheic keratosis may be observed in women with seborrheic keratosis on the neck, face, or trunk. Typically, seborrheic keratoses are slightly raised, sharply circumscribed verrucous lesions with a dark greasy appearance. The malignant potential of these slow-growing lesions is minimal. Therefore excision is offered only in cases of discomfort or disfigurement.

Keratoacanthoma

Keratoacanthomas are rapidly growing low-grade malignancies originating in pilosebaceous glands. Lesions begin as firm, round papules that progress to dome-shaped nodules with central craters. Untreated, the lesions will spontaneously regress within 4 to 6 months, leaving only a slightly depressed scar. Given its slight malignant potential and its resemblance to squamous cell carcinoma, surgical excision with 3- to 5-mm margins is recommended.

LEIOMYOMA

Vulvar leiomyomas are extremely rare tumors felt to arise from either smooth muscle within the vulva's erectile tissue or transmigration through the round ligament. Surgical excision to exclude leiomyosarcoma is warranted (Nielsen, 1996).

FIBROMA

Fibroma is a rare benign tumor of the vulva with a reported incidence of 0.03 percent (Chen, 2004). Fibromas arise from deep connective tissues by proliferation of fibroblasts. Lesions are primarily found on the labium majus, and range in size from 0.6 to 8 cm in diameter. Larger lesions often become pedunculated with a long stalk and may cause pain or dyspareunia. Surgical excision is the primary treatment for symptomatic lesions.

LIPOMA

A large, soft sessile or pedunculated mass composed of mature adipose cells is termed *lipoma* . Similarly to fibromas, observation is reasonable in the absence of patient complaints, whereas symptoms may prompt surgical excision. These lesions lack a fibrous connective tissue capsule and complete dissection may be complicated by bleeding requiring a larger incision. Accordingly, surgical excision in an outpatient surgical unit with appropriate anesthesia and instruments is prudent.

Cystic Vulvar Tumors

BARTHOLIN GLAND DUCT CYST AND ABSCESS

Mucus produced to moisten the vulva originates in part from the Bartholin glands. Obstruction of this gland's duct can lead to cystic enlargement that accounts for nearly 2 percent of all new gynecologic visits (Fig. 4-9). Cysts may become infected, and the purulent contents result in abscess development.

FIGURE 4-9

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Bartholin gland duct cyst seen as an asymmetric bulge on the left (the patient's right). *(Courtesy of Dr. William Griffith.)*

PATHOPHYSIOLOGY

Infection

Bartholin duct cysts form in direct response to obstruction of ductal outflow. Despite this understanding, the primary reason for cyst formation remains unknown. Abscess formation tends to develop in populations with demographic profiles similar to those at high risk for sexually transmitted infections (Aghajanian, 1994). Historically, women with bilateral Bartholin gland duct cysts were assumed to have been infected with *Neisseria gonorrhoeae* . However, resent studies have demonstrated a wider spectrum of organisms responsible for these cysts and abscesses. For example, Tanaka and colleagues (2005) examined 224 patients and approximately two bacterial species per case were isolated. A majority were caused by aerobic bacteria, of which *Escherichia coli* was the most common isolate. Interestingly, only five cases involved *N gonorrhoeae* or *Chlamydia trachomatis* (Tanaka, 2005).

Other theories for ductal obstruction include a change in mucus consistency, mechanical trauma from poorly repaired episiotomies, or even congenitally narrowed ducts. Since mucus retention leads to cyst distention, the size and speed of growth are influenced by sexual stimulation. Hence, rapid accumulation is observed during times of heightened sexual excitement.

Malignancy

After menopause, Bartholin gland duct cysts and abscesses are uncommon and should raise suspicion of neoplasia. Carcinoma of the Bartholin gland is rare, and its incidence approximates 0.1 per 100,000 women (Visco, 1996). A majority of lesions are squamous carcinomas or adenocarcinomas (Copeland, 1986).

Given the rarity of these cancers, Bartholin gland excision is typically not indicated. Alternatively, in women older than 40 years, drainage of the cyst and biopsy of suspicious cyst wall sites adequately excludes malignancy (Visco, 1996).

Symptoms

Most Bartholin gland cysts are small and asymptomatic except for minor discomfort during sexual arousal. When a lesion becomes larger or infected, women may experience severe vulvar pain the precludes them from walking, sitting, or engaging in sexual activity.

Diagnosis

A Bartholin gland enlargement can mimic several other vulvovaginal masses. Most cysts are unilateral, round or ovoid, and tense. Abscesses typically display surrounding erythema and are tender to palpation. The mass is usually located in the posterior labia majora or lower vestibule. Whereas most cysts and abscesses lead to asymmetry of labial anatomy, some smaller cysts may only be detected by palpation. Bartholin abscesses on the verge of spontaneous decompression will exhibit an area of softening where rupture will most likely occur.

Treatment

Small, asymptomatic cysts require no intervention except to exclude neoplasia in women older than 40 years. Multiple techniques exist for managing cysts that cause significant pressure symptoms or become infected. These include incision and drainage, marsupialization, and Bartholin gland excision, and are described and illustrated in Sections 41-6, Bartholin Gland Duct Incision and Drainage through 41-8, Bartholinectomy.

SKENE GLAND CYST AND ABSCESS

Ductal occlusion of the Skene gland, which is the largest paraurethral gland and located at the distal urethra, may lead to cystic enlargement and possible abscess formation (Chap. 26, Classification). Its etiology remains unknown, although many speculate that infection or trauma may predispose.

The main symptoms include urinary obstruction, dyspareunia, and pain. The primary treatment for these insignificant glandular enlargements is excision. In the presence of an acute abscess, a lesion should not be excised until infection subsides.

URETHRAL DIVERTICULUM

This is a cystic enlargement of a paraurethral gland. Typically found along the inferior urethral wall, these sacs communicate directly with the urethra and bulge into the anterior vaginal wall (see Fig. 26-3) (Lee, 2005). Although postvoid dribbling is a classic complaint, women may also note pain, dyspareunia, or urinary symptoms. On physical examination, a urethral diverticulum may be palpated as a slight bogginess along the length of the urethra. Urine or purulent drainage can be expressed with compression. Urethral diverticula are discussed further in Chapter 26, Urethral Diverticulum and their surgical management illustrated in Section 42-9, Urethral Diverticulum Repair.

VULVAR EPIDERMAL INCLUSION CYST

These are common vulvar cysts, often termed sebaceous cysts, which result from folding of the squamous vulvar epithelium beneath the epidermis. They are firm, mobile, nodular lesions, and are filled with white or yellow caseous material.

In general, inclusion cysts are asymptomatic and require no therapy. Symptomatic, noninfected lesions, may be removed by wide excision of the entire cyst or by punch biopsy of the lesion with extrusion of cyst contents and cyst wall through the biopsy opening (Moore, 2007). Lee and colleagues (2006) found similarly low recurrence rates and superior healing with the punch technique in a randomized prospective study of 60 patients.

Vulvodynia

In October 2003, the 17th ISSVD World Congress unanimously agreed upon defining vulvodynia as "vulvar discomfort, most often described as burning pain, occurring in the absence of relevant visible findings or a specific, clinically identifiable, neurologic disorder" (Table 4-8) (Moyal-Barracco, 2004). The pain of vulvodynia is described as spontaneous (unprovoked) or triggered by physical pressure (provoked) such as sexual contact, tampon insertion, or fingertip pressure. In addition, the term *vestibulitis* was eliminated from ISSVD terminology since inflammatory changes have not been consistently documented.

Table 4-8 International Society for the Study of Vulvovaginal Disease (2003) Terminology and Classification of Vulvar Pain
A. Vulvar pain related to a specific disorder ■ Infectious ■ Inflammatory ■ Neoplastic ■ Neurologic
B. Vulvodynia ■ Generalized ■ Provoked ■ Unprovoked ■ Mixed
C. Localized (vestibulodynia, clitorodynia, hemivulvodynia, etc.) ■ Provoked ■ Unprovoked ■ Mixed

Modified from Moyal-Barracco, 2004, with permission.

INCIDENCE

Unfortunately, limited information is available regarding the number of women with vulvodynia. This can be explained in part by an average delay of 4 years before reaching the appropriate diagnosis, and by patient underreporting secondary to psychosexual embarrassment (Graziottin, 2004). In a population study by Harlow and Stewart (2003), 55 percent of women with chronic vulvar pain sought treatment. Of those that did, more than 60 percent saw three or more doctors, many of whom were unable to provide an accurate diagnosis. Hispanic women are 80 percent more likely to experience chronic vulvar pain compared with African-American and Caucasian women. There is a wide age variation in prevalence patterns.

ETIOLOGY OF VULVODYNIA

The precise etiology of vulvodynia is unknown. Although many factors have been investigated, most agree that the process is multifactorial and requires an interdisciplinary approach to treatment (Babula, 2004; Bouchard, 2002; Danielsson, 2001).

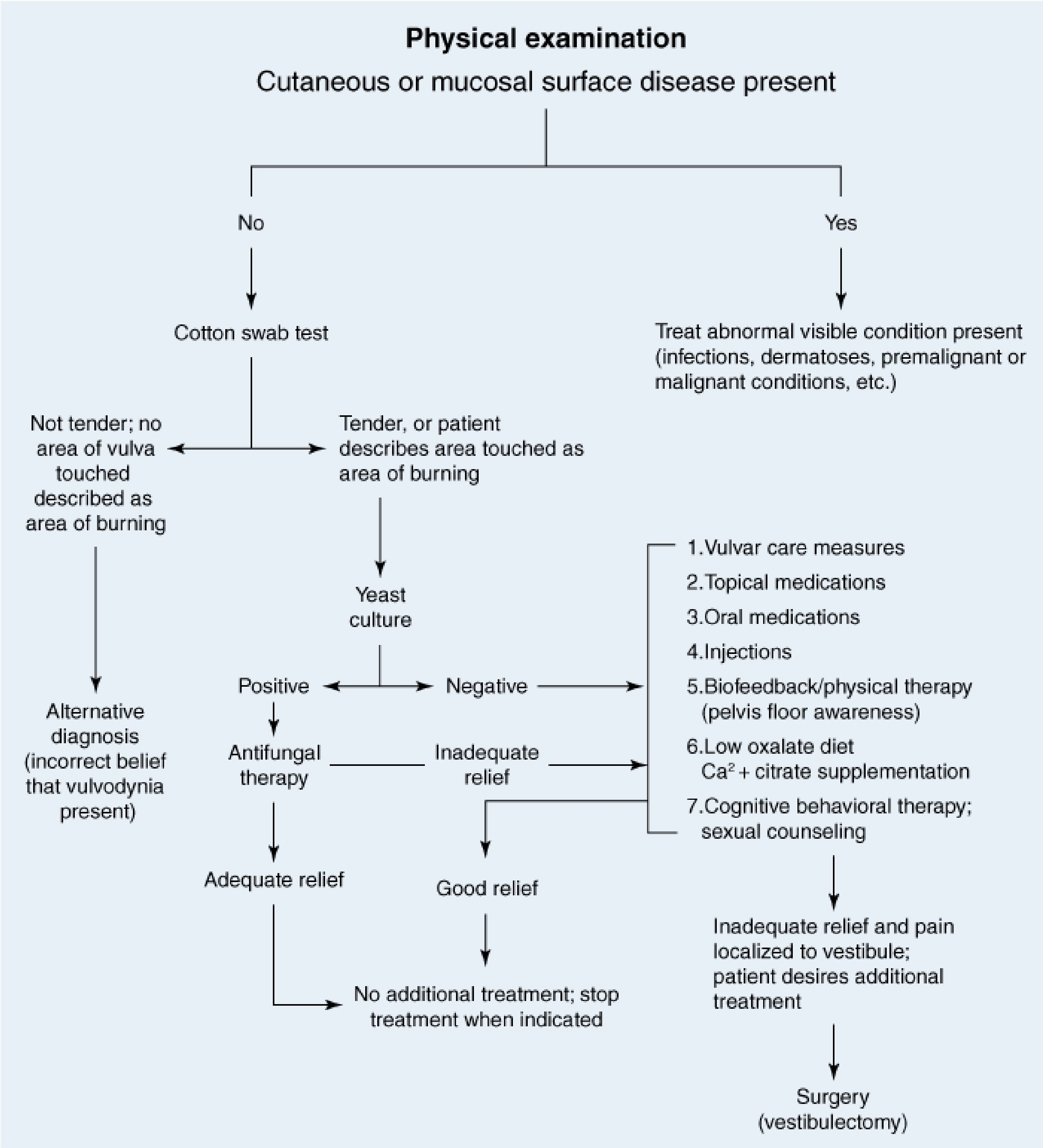
NEUROPATHIC CHANGES

Serotonin-containing neuroendocrine cells are found at multiple sites in the female genital tract. Substance P axons have been demonstrated in the ducts of vestibular glands in close proximity to these cells. This is an important association for two reasons. First, neurogenic inflammation through increased vascular permeability and vasodilatation are felt to be mediated by substance P and serotonin. Evidence of increased blood flow to the most painful area on the vestibular mucosa has been documented using laser Doppler perfusion imaging (Bohm-Starke, 2001). Second, this association may explain the pinpoint tenderness of vestibular glands in those with vulvodynia in the absence of other physical findings (Warner, 1996).

DIAGNOSIS

An evidence-based algorithm for the diagnosis of vulvodynia is provided in Fig. 4-10 (Haefner, 2005). Given that vulvodynia is a diagnosis of exclusion, an extensive history is critical to securing the correct diagnosis.

FIGURE 4-10



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Algorithm for the diagnosis of vulvodynia. *(From Haefner, 2005, with permission.)*

Symptoms of Vulvodynia

Vulvodynia refers to vulvar discomfort of at least 3 to 6 months' duration without an identifiable cause (Table 4-9). The location and temporal pattern of dyspareunia can help predict the physical diagnosis (Meana, 1997). Many women with localized vulvodynia may describe burning, itching, or cutting pain within affected areas (Bergeron, 2001). Pain may follow a touch stimulus (allodynia) such as wearing tight clothing or undergarments or undergoing pelvic examination. Sensations are intermittent and even episodic with exacerbations noted premenstrually (Arnold, 2006).

Table 4-9 Questions Appropriate for Investigation of Vulvodynia

1. *When* did the pain begin? Was it sudden? Was there a sentinel event?
2. *How* did the pain begin? Was it gradual? Acute? Spontaneous?
3. *Describe* the pain? Is it Localized? General? Provoked? Unprovoked? How intense is it?
4. *Aggravating* factors? Position? Touch?
5. *Relieving* factors? Prior therapy?
6. *Associated* symptoms? Urinary? Skin complaints? Itching?
7. *Impact* of the pain?

This can help provide clear goals for treatment and serve as a point of reference to assess therapy.

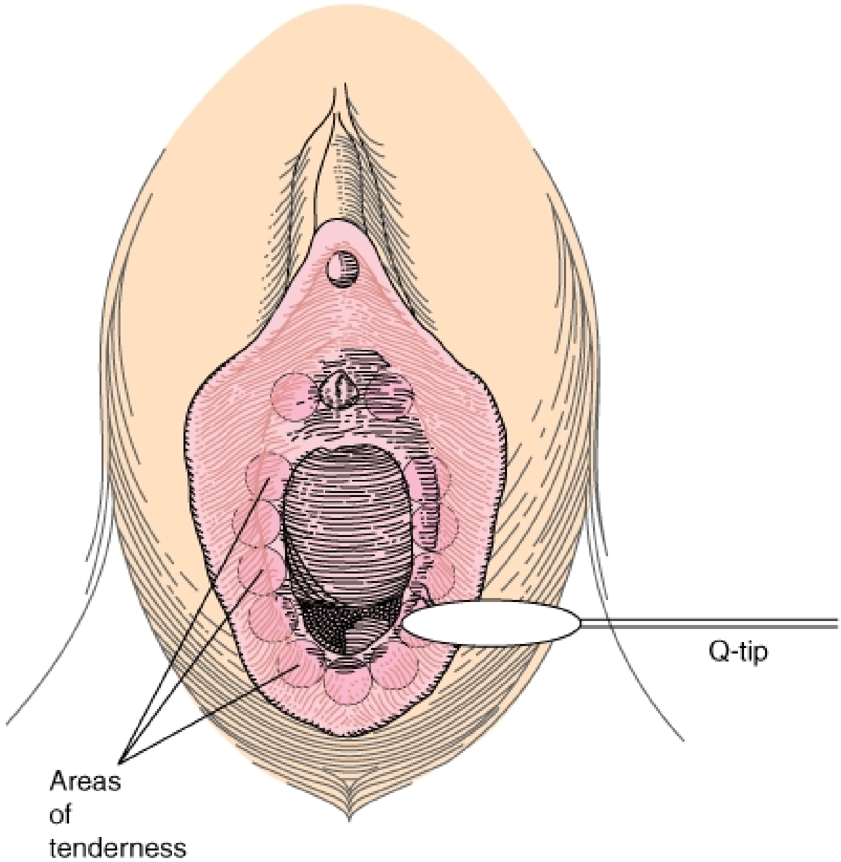
Questioning should seek to identify frequently associated comorbid conditions or other risk factors, such as irritable bowel syndrome, interstitial cystitis, psychological disorders, relationship discord, or prior infectious disease such as herpes simplex or zoster (Arnold, 2007). Documentation of past surgical procedures may help identify injury to the pudendal nerve. A sexual history may reveal clues of past or current abuse, unfavorable coital patterns, and contraceptive preferences that could provoke vulvodynia. Additionally, clinicians should inquire about recurrent candidiasis; prior genital trauma, including childbirth-related injuries; and current hygienic practices, including the use of feminine products, panty liners, soaps, undergarment fabrics, and perfumes. Importantly, prior therapies should be documented to avoid unnecessary treatment repetition.

Physical Examination

By definition, vulvodynia lacks identifying physical markers. Therefore a thorough examination is first required to exclude other possible pathologies. Inspection of the external vulva is followed by examination of the vestibule tissue to search for foci of erythema. Colposcopic investigation of the vulva and directed biopsies will exclude other pathology (see Chap. 29, Colposcopy).

Systematic pain mapping of the vestibule, perineum, and inner thigh is completed and serves as a reference to assess treatment success (Fig. 4-11). A cotton swab is used to check for allodynia and hyperesthesia. The end can first be unwound to form a cotton-fiber wisp. Subsequently, the wooden stick is broken to form a sharp point to retest the same areas. The severity of pain on a five- or ten-point scale should be recorded and followed over time.

FIGURE 4-11



Pain can be assessed and mapped by systematically touching a cotton-tipped applicator to the vulva. *(From Howard, 2000, with permission.)*

Laboratory Testing

Although no specific laboratory test can diagnose vulvodynia, a wet prep of vaginal secretions, vaginal pH evaluation, yeast subtyping, and bacterial markers are helpful in excluding underlying vaginitis (see Table 3-15). Ulcerative lesions should prompt biopsy consideration and cultures for herpes simplex virus. Herpes viral serology may prove helpful but patient counseling regarding the interpretation of results is recommended.

TREATMENT

In the absence of well-designed clinical trials, no specific therapy for vulvodynia is deemed superior. In general, a combination of multiple medical forms of therapy may be required to stabilize and improve patient symptoms. In the absence of improvement with medical treatment, surgical excision is a final option.

MEDICAL THERAPY

Vulvar Care

The first step in managing all vulvar disorders includes gentle vulvar care. As shown in Table 4-2, cotton undergarments, avoidance of vulvar irritants, restoration of the barrier function, and appropriate lubrication during intercourse are the mainstays of vulvar care (Haefner, 2005).

Biofeedback and Physical Therapy

If components of back pain, muscle spasm, or vaginismus are present, a trained vulvar physical therapist can improve symptoms and coital frequency through use of internal and external massage, myofascial release techniques, acupressure, and pelvic floor retraining (Bergeron, 2002).

Behavioral Therapy

Many believe vulvodynia is more than a psychosexual problem. Compared with the general population, no differences in marital contentment or psychological distress are found (Bornstein, 1999). Nevertheless, early counseling should include a basic assessment of sexual function and offer education regarding foreplay, sexual positions, lubrication, and alternatives to vaginal intercourse.

Topical Medications

A generous amount of 5-percent lidocaine ointment applied to the vestibule 30 minutes prior to sexual intercourse has been shown to significantly decrease dyspareunia (Zolnoun, 2003). Long-term use may lead to healing by minimizing feedback pain amplification (see Chap. 11, Neuropathic Pain). Numerous other topical anesthetic preparations have been used and reported to have variable success. Particular caution, however, should be exercised with benzocaine, which has been associated with increased rates of contact dermatitis.

Eva and colleagues (2003) found decreased estrogen receptor expression in women with vulvodynia. However, topical or intravaginal estrogen therapy has yielded mixed results.

Oral Medications

The two major classes of oral medications found to help in the treatment of vulvodynia are antidepressants and anticonvulsants.

Tricyclic antidepressants (TCAs) have become first-line agents in the treatment of vulvodynia. Reported response rates to TCAs may reach 47 percent (Munday, 2001). In our experience, amitriptyline started between 5 and 25 mg orally nightly and increased as needed by 10 to 25 mg weekly, yields the best results (see Table 11-5). Final daily doses should not exceed 150 to 200 mg. Importantly, women should remain compliant despite the nearly 4-week lag required to achieve significant pain relief.

Cases resistant to TCAs may be treated with the anticonvulsants, gabapentin, or carbamazepine (see Table 11-5) (Ben David, 1999). Gabapentin is initiated at a dosage of 100 mg orally three times daily and gradually increased within 6 to 8 weeks to a maximum daily dose of 3600 mg. Once this dose is reached, pain may be reassessed after 1 to 2 weeks (Haefner, 2005).

Intralesional Injections

In cases of localized vulvodynia, trigger point injections using a combination of steroids and anesthetics, such as a mixture of a 4:1 ratio of methylprednisolone acetate and lidocaine cloridrate, can be injected directly into the lesion (Murina, 2001).

Surgical Therapy

Women with vulvodynia who fail to improve clinically despite aggressive medical therapy are candidates for surgical intervention. Options include local excision of a precise pain locus; complete resection of the vestibule, termed *vestibulectomy* ; or resection of the vestibule and perineum, known as *perineoplasty* . These are illustrated in Section 41-9, Vestibulectomy. Traas and colleagues (2006) reported high success rates with vestibulectomy among women less than 30 years of age. Perineoplasty is the most extensive of the three procedures, and the incision extends from just below the urethra to the perineal body, usually terminating above the anal orifice. This procedure may be selected if significant perineal scarring is suspected to contribute to dyspareunia.

Congenital Lesions

Structural congenital abnormalities of the lower reproductive tract are uncommon and include those resulting from organ atresia, failure of tissues to regress or to fuse normally, and abnormal hormone signaling. These are discussed in detail in Chapter 18.

Infectious Lesions

Infection is a common cause of benign vulvar disease and may involve bacteria, fungi, viruses, or parasites. Ulcerative, proliferative, or suppurative lesions may result, and each is discussed in Chapter 3.

Preinvasive and Malignant Disease

Cancerous and preinvasive neoplasias of the vulva are uncommon and typically are found as unifocal lesions in older women. However, significant rises in human papillomavirus-related multifocal vulvar intraepithelial neoplasia (VIN) have recently been noted in younger women. Symptoms are variable and may include severe pruritus, pain, and dyspareunia. Because a well-defined mass is not always present, vulvar areas with thickened epithelium or persistent areas of ulceration, pain, or pruritus should prompt biopsy. Most neoplastic lesions are of squamous cell origin and carry a favorable prognosis if identified and treated early (see Chaps. 29, Vulvar Preinvasive Lesions and 31, Lymph Node Metastasis).

Vulvovaginal Trauma

BLUNT TRAUMA

Given the anatomic location and adipose padding of the labia majora, accidental vulvar and vaginal injuries are rare. Conversely, as children lack such well-developed fat pads in the labial area, objects such as bicycle bars, gymnastics beams, and bench rails may increase their risk of straddle injuries (Virgili, 2000). The usual sequela of blunt trauma to the vascularly-rich vulva is a hematoma.

Often requiring a general anesthetic, a thorough examination of the vulva and vagina will allow estimation of the stability and size of the hematoma, and the integrity of the surrounding organs such as the bowel, bladder, urethra, and rectum. Fortunately, if no associated organ injury is noted, the venous nature of vulvar hematomas make them candidates for conservative management with cool pack, Foley drainage of the bladder, and adequate pain control (Propst, 1998).

Vaginal hematomas larger than 4 cm should be explored surgically in search of bleeding vessels to secure. An unstable patient may result from retroperitoneal bleeding from a retracted vessel (Gianini, 1991). Postoperatively, a vaginal pack may help tamponade any venous leakage.

LACERATION

Penetrating trauma accounts for most vaginal injuries. Common causes of trauma include pelvic fracture, forced inanimate objects, coitus, and hydraulic forces such as those experienced with water skiing (Smith, 1996).

Examination under anesthesia is often necessary to perform a thorough assessment and to exclude intraperitoneal damage. Treatment goals include achieving hemostasis and restoration of normal anatomy. Irrigation, dÃ©bridement, and primary repair are desirable. On occasion, infection may require allowing a laceration to close by secondary intent. Ultimately, techniques for repairing vulvovaginal trauma are similar to those used for obstetric lacerations.

If the peritoneal cavity has been breached, a transabdominal exploration by either laparotomy or laparoscopy is mandatory to exclude inadvertent visceral injury.

SEXUAL INJURY

Differentiating straddle injury and sexual abuse is often challenging, as injury patterns do not accurately confirm or exclude sexual trauma. Diagnosis requires careful inquiry and correlation of described mechanisms of injury with physical examination findings.

Certain characteristics may serve as red flags for sexual abuse. In an infant or child, these include extensive trauma and injury at an extragenital site, genital secretions, lack of correlation between history and physical examination, or condyloma acuminata (Dowd, 1994; Emans, 1987). Moreover, injuries to the posterior fourchette; those of the hymen that extend from 3 to 9 o'clock; or vaginal, rectal, or peritoneal perforation should increase suspicion for sexual abuse (Bond, 1995).

In contrast, a unilateral, single, or stellate laceration or bruise in the same shape as that of the described blunt object supports a diagnosis of unintentional injury. In addition, nonpenetrating straddle injuries are more common in unintentional settings. Thus, lacerations or abrasions of the labia minora, mons pubis, and clitoris that are anterior or lateral to the hymen are typical of straddle injury.

VAGINAL LESIONS

Foreign Bodies

Vulvovaginal injuries may result from trauma caused by a foreign body placed into the vagina. Although seen in women of all ages, the nature of the object varies with the affected population. For example, small objects may lodge in a child's vagina during play or self-exploration or an adolescent may complain of being unable to retrieve a forgotten tampon or broken condom. Sexual misadventure or abuse can usually explain the etiology of objects found in adult women. Two items in particular warrant further discussion: the forgotten tampon and vaginal pessary.

Women with a forgotten tampon will typically complain of a foul-smelling vaginal discharge with some associated pruritus, discomfort, or dysfunctional bleeding. After further discussion, a history of multiple unsuccessful retrieval attempts may be revealed. In the absence of a leukocytosis, fever, or evidence of an endometritis or salpingitis, simple removal of the tampon is appropriate. Vaginal lavage to clean the vagina is not indicated, as it may actually increase the risk of ascending infection.

Vaginal pessaries are commonly used for the conservative treatment of pelvic organ prolapse (see Chap. 24, Types of Pessaries). Atrophic vaginal epithelium increases the risk of ulcerative or erosive complications with inappropriately sized devices. Intravaginal estrogen cream and close physician assessments with periodic removal are essential in avoiding such injuries. Complaints of bloody or foul-smelling discharge should warrant an immediate inspection of the vaginal vault.

Epidermal Inclusion Cysts

A collection of desquamated epithelial cells encapsulated by a wall of stratified squamous epithelium in the dermis of the vagina is known as an epidermal inclusion cyst. Inclusion cysts are variable in size and are visible through the vaginal mucosa as round white masses. Generally, the cyst is filled with viscous, gritty, or caseous foul-smelling contents that closely resemble a purulent exudate. As with those found in the vulva, epidermal inclusion cysts are generally asymptomatic and require no further evaluation except in the case of infection, in which incision and drainage are recommended.

Diethylstilbestrol-Induced Reproductive Tract Abnormalities

In the mid-1900s, diethylstilbestrol (DES), a synthetic nonsteroidal estrogen, was prescribed for a number of pregnancy problems to women in the United States (see Chap. 18, Acquired Uterine Defects). These women's daughters, who were exposed in utero to DES, showed increased rates of vaginal clear cell adenocarcinoma and congenital reproductive tract changes (Herbst, 1971). These changes included transverse vaginal septums, circumferential ridges involving the vagina and cervix, and cervical collars (see Fig. 32-7). Additionally, areas of columnar epithelium within the vaginal squamous mucosa may be found in these women, and is termed *vaginal adenosis* . Vaginal adenosis typically appears red, punctuate, and granular. Common symptoms and signs include vaginal irritation, discharge, and metrorrhagia, in particular postcoital bleeding.

Gartner Duct Cyst

These uncommon vaginal cysts develop from remnants of the mesonephric (Wolffian) ducts (see Fig. 18-2). They are typically asymptomatic and are usually found within the lateral vaginal wall during routine examination. Symptoms, however, may include dyspareunia, vaginal pain, and obstruction to insertion of tampons or other vaginal devices. Examination reveals a tense cyst that is palpable or seen to bulge beneath the vaginal wall. Observation alone is reasonable in most cases, although marsupialization or excision may be appropriate for symptomatic Gartner duct cysts.

CERVICAL LESIONS

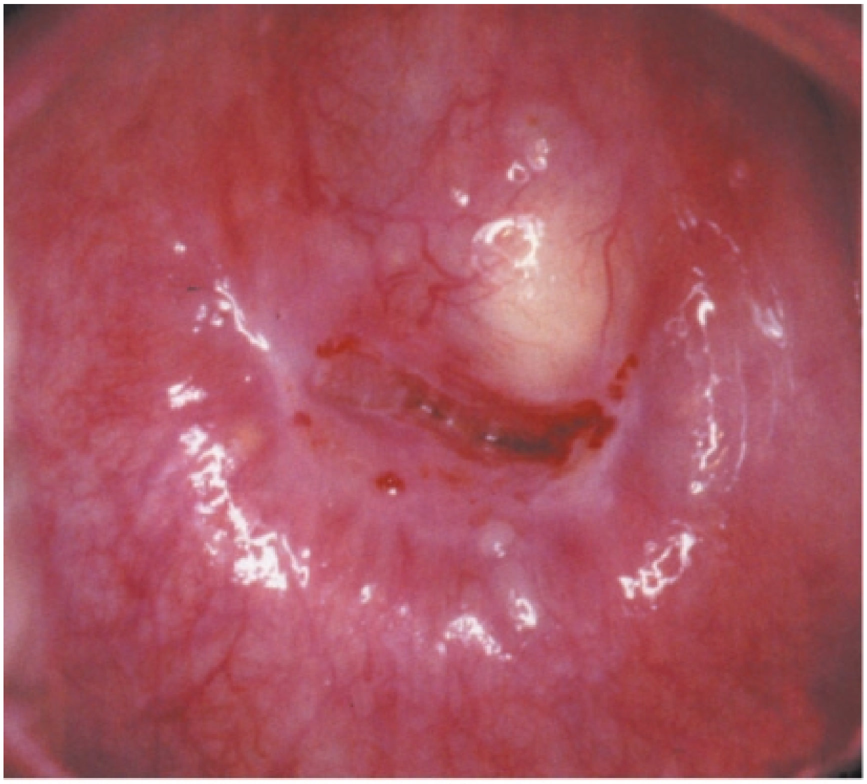
Eversion

The squamocolumnar junction (SCJ) is the border between the columnar epithelium of the endocervix and the squamous epithelium of the ectocervix. Endocervical tissue in some women may move out from the endocervical canal in a process termed eversion (see Fig. 29-2). As a result, the SCJ lies further from the external cervical os. To perform an adequate Pap smear, the clinician must identify the circumferential path of the SCJ prior to sampling.

Nabothian Cyst

Mucus-secreting columnar cells line the endocervical canal. During squamous metaplasia, squamous epithelium may cover nests of glandular cells, predisposing them to accumulation of secretions. As this benign process continues, smooth, clear or yellow glandular elevations are visible during routine examination (Fig. 4-12). Nabothian cysts warrant no further therapy.

FIGURE 4-12



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Cervical nabothian cyst. *(From O'Connor, 2002, with permission.)*

Endocervical Polyp

One of the most common benign neoplasms of the cervix is a hyperplastic projection of the endocervical folds known as an *endocervical polyp* (Fig. 4-13). Lesions are easily found during routine cervical surveillance and may be associated with leukorrhea or postcoital spotting. In the presence of a slender stalk, polyp removal may be accomplished by a continuous twisting of the lesion with ring forceps. Twisting leads to occlusion of supporting vessels and avulsion of the mass. A thick-pedicled polyp is best treated by surgical excision. Excised cervical polyps require pathologic evaluation to exclude malignancy.

FIGURE 4-13

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Soft fleshy endocervical polyp seen prolapsing from the endocervical canal. *(From Mestwerdt, 1981, with permission.)*

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CONTRACEPTION AND STERILIZATION: INTRODUCTION

A wide variety of effective methods of regulating fertility is currently available. None is completely without side effects or categorically without dangerâ€"for example, latex condoms can cause anaphylactic reactions. That said, and as shown in Table 5-1, contraception poses less risk than does pregnancy. In fact, for most women it is safer to use contraception than it is to drive a car (Hatcher, 2004).

Table 5-1 Birth-Related or Method-Related Deaths Per 100,000 Fertile Women by Age Group

Method	15â€"24 Yrs	25â€"34 Yrs	35â€"44 Yrs
Pregnancy	5.1	5.5	13.4
Abortion	2.0	1.8	13.4
Intrauterine device	0.2	0.2	0.4
Rhythm, withdrawal	1.3	1.0	1.3
Barrier method	1.0	1.3	2.0
Spermicides	1.8	1.7	2.1
Oral contraceptives	1.1	1.5	1.4
Implants/injectables	0.4	0.6	0.5
Tubal sterilization	1.2	1.1	1.2
Vasectomy	0.1	0.1	0.1

Modified from Harlap, 1991, with permission.

CONTRACEPTION

Pregnancy rates at 1 year approach 90 percent for sexually active fertile women who do not use contraception. Because ovulation often precedes menstruation, young women should be advised to use contraception whenever they begin sexual activity. Providing contraceptive advice for the woman nearing menopause is harder, because it is difficult to predict when fertility has ended.

Contraceptive Methods

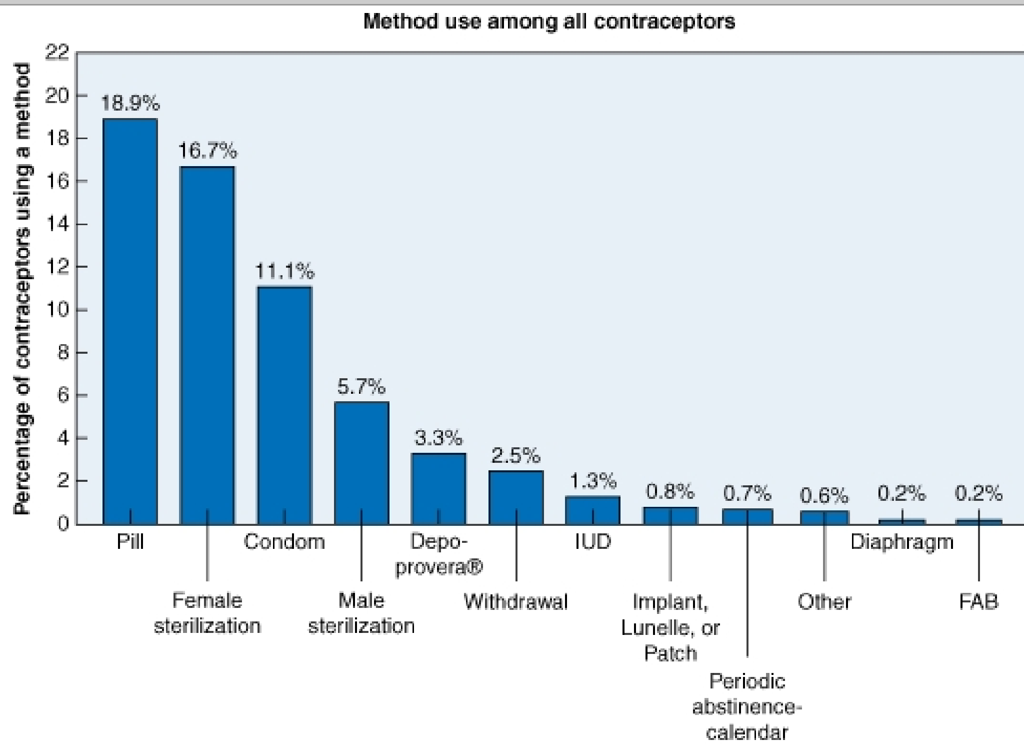
Methods of variable effectiveness currently employed in the United States include:

- Oral steroidal contraceptives
- Injected steroidal contraceptives
- Intrauterine devices

- Transdermal and transvaginal steroidal contraceptives
- Physical, chemical, or barrier techniques
- Sexual abstinence around the time of ovulation
- Breast feeding
- Permanent sterilization

The most recent nationally representative data concerning contraceptive use were collected in 1995 (Fig. 5-1). Additionally, in 2002, Bensyl and associates (2005) reported results from the Behavior Risk Factor Surveillance System (BRFSS). Although results varied, sometimes substantially, across states as well as by gender and ethnic group, the methods generally reported were similar to those shown in Table 5-1.

FIGURE 5-1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Contraceptive use in the United States circa 1995 for users aged 15 to 44 years. FAB = fertility awareness-based method; IUD = intrauterine device.

Based on the results of the 1995 National Survey of Family Growth, approximately one thirdâ€"2.65 millionâ€"of all pregnancies were unintended. Indeed, half of unintended pregnancies were in women using a method of contraception at the time of conception (Henshaw, 1998). Estimates of the failure rate during the first year of use are given in Table 5-2.

Table 5-2 Contraceptive Failure Rates during the First Year of Use

	Percent of Women with Pregnancy	
Method	**Perfect Use (%)**	**Typical Use (%)**

None	85	85
Combination pill	0.3	8
Progestin-only pill ("mini-pill")	0.5	8
Intrauterine devices		
Mirena levonorgestrel device	0.1	0.1
ParaGard T 380A	0.6	0.8
Combination Patch	0.3	8
Depot medroxyprogesterone	0.3	3.1
Combination injectable	0.5	3
Levonorgestrel implants	0.05	0.05
NuvaRing vaginal ring	8	0.3
Female sterilization	0.5	0.5
Male sterilization	0.1	0.15
Spermicides	18	29
Periodic abstinence:		
Calendar	9	20
Ovulation method	3	
Symptothermal	2	
Post ovulation	1	
Withdrawal	4	27
Cervical cap		
Parous women	26	32
Nulliparous women	9	16
Sponge		
Parous women	20	32
Nulliparous women	9	16
Diaphragm and spermicides	6	16
Condoms		

Male	2	15
Female	5	21
Emergency contraception	>75% reduction	

Data from Speroff, 2001, and Trussell, 2004, with permission.

Obviously, the importance of accurate, timely, and complete counseling and education regarding correct product use is essential to the contraceptive efficacy of any method. The large number of unintended pregnancies in women using contraception is evidence of deficits in contraception dispensing, prescribing, and education. Because of this, many women have misperceptions about the risks of contraception use, as well as how to effectively implement them (Picardo, 2003). According to Dailard (2005), if comprehensive sex education was provided, a 40-percent decrease in unintended pregnancies could be achieved.

HORMONAL CONTRACEPTIVES

These types of contraceptives are currently available in a wide variety of forms: pill, injection, transdermal patch, implant, and a transvaginal ring. Combination oral contraceptivesâ€”"The Pill"â€”consist of a combination of estrogen and progestin, or a progestin only pillâ€”the *mini-pill.* Other forms contain progestins alone or a combination of estrogen and progestin. Unfortunately, no reliable reversible male hormonal contraceptives have been developed (Kamischke, 2004).

Estrogen Plus Progestin Contraceptives

Combination oral contraceptives (COCs) are the most frequently used method of hormonal contraception, and an almost bewildering variety are marketed (Table 5-3). Although generic formulations accounted for only 3.6 percent of prescriptions in 1990, they accounted for 18 percent by 2001 (Keith, 2001).

Table 5-3 Oral Contraceptives Available in the United States

Product Name	**Manufacturer**	**Estrogen**	**µg**	**Progestin**	**mg**
Monophasic preparations					
20 µg Estrogen					
Alesse	Wyeth-Ayerst	EE	20	Levonorgestrel	0.10
Levlite	Berlex	EE	20	Levonorgestrel	0.10
Loestrin 1/20	Parke-Davis	EE	20	Norethindrone acetate	1.00
30â€“35 µg Estrogen					
Desogen	Organon	EE	30	Desogestrel	0.15
Levlen	Berlex	EE	30	Levonorgestrel	0.15
Levora	Watson	EE	30	Levonorgestrel	0.15
Lo/Ovral	Wyeth-Ayerst	EE	30	Norgestrel	0.30
Low-Ogestrel	SCS Pharmaceuticals	EE	30	Norgestrel	0.30
Nordette	Wyeth-Ayerst	EE	30	Levonorgestrel	0.15

Ortho-Cept	Ortho-McNeil	EE	30	Desogestrel	0.15
Brevicon	Searle	EE	35	Norethindrone	0.50
Demulen 1/35	Searle	EE	35	Ethynodiol diacetate	1.00
Loestrin 1.5/30	Parke-Davis	EE	30	Norethindrone acetate	1.50
Modicon	Ortho-McNeil	EE	35	Norethindrone	0.50
Necon 0.5/35	Watson	EE	35	Norethindrone	0.50
Necon 1/35	Watson	EE	35	Norethindrone	1.00
Nelova 0.5/35E	Warner Chilcott	EE	35	Norethindrone	0.50
Nelova 1/35E	Warner Chilcott	EE	35	Norethindrone	1.00
Norinyl 1+35	Searle	EE	35	Norethindrone	1.00
Ortho-Cyclen	Ortho-McNeil	EE	35	Norgestimate	0.25
Ortho-Novum 1/35	Ortho-McNeil	EE	35	Norethindrone	1.00
Ovcon-35	Bristol-Myers Squibb	EE	35	Norethindrone	0.40
Zovia 1/35E	Watson	EE	35	Ethynodiol diacetate	1.00
50 µg Estrogen					
Ovral	Wyeth-Ayerst	EE	50	Norgestrel	0.50
Demulen 1/50	Searle	EE	50	Ethynodiol diacetate	1.00
Necon 1/50	Watson	Mes	50	Norethindrone	1.00
Nelova 1/50M	Warner Chilcott	Mes	50	Norethindrone	1.00
Norinyl 1+50	Searle	Mes	50	Norethindrone	1.00
Ortho-Novum 1/50	Ortho-McNeil	Mes	50	Norethindrone	1.00
Ovcon 50	Bristol-Myers Squibb	EE	50	Norethindrone	1.00
Zovia 1/50E	Watson	EE	50	Ethynodiol diacetate	1.00
Multiphasic preparations					
20 µg Estrogen					
Mircette	Organon	EE	20 (21)	Desogestrel	0.15
			0 (2)		
			10 (5)		

30â€"35 µg Estrogen					
Ortho Tri-Cyclen	Ortho-McNeil	EE	35 (21)	Norgestimate	0.18 (7)
					0.215 (7)
					0.25 (7)
Tri-Levlen	Berlex	EE	30 (6)	Levonorgestrel	0.05 (6)
			40 (5)		0.075 (5)
			30 (10)		0.125 (10)
Triphasil	Wyeth-Ayerst	EE	30 (6)	Levonorgestrel	0.05 (6)
			40 (5)		0.075 (5)
			30 (10)		0.125 (10)
Trivora	Watson	EE	30 (6)	Levonorgestrel	0.05 (6)
			40 (5)		0.075 (5)
			30 (10)		0.125 (10)
Estrostep	Parke-Davis	EE	20 (5)	Norethindrone acetate	1.00
			30 (7)		
			35 (9)		
Estrostep Fe	Parke-Davis	EE	20 (5)	Norethindrone acetate	1.00
			30 (7)		
			35 (9)		
Jenest	Organon	EE	35 (21)	Norethindrone	0.50 (7)
					1.00 (14)
Necon 10/11	Watson	EE	35 (21)	Norethindrone	0.50 (10)
					1.00 (11)
Nelova 10/11	Warner Chilcott	EE	35 (21)	Norethindrone	0.50 (10)
					1.00 (11)
Ortho-Novum 7/7/7	Ortho-McNeil	EE	35 (21)	Norethindrone	0.5 (7)
					0.75 (7)
					1.00 (7)

Tri-Norinyl	Searle	EE	35 (21)	Norethindrone	0.5 (7)
					1.00 (9)
					0.50 (5)
Progestin-only preparations					
Ovrette	Wyeth-Ayerst	None		Norgestrel	0.075 (c)
Micronor	Ortho-McNeil	None		Norethindrone	0.35 (c)
Nor-QD	Watson	None		Norethindrone	0.35 (c)
Extended-cycle preparation					
Seasonale[a]	Barr	EE	30 (84)	Levonorgestrel	0.15 (84)
Seasonique[b]	Barr	EE	30 (84)	Levonorgestrel	0.15 (84)
			10 (7)		

(c) = continuous use; EE = ethinyl estradiol; Mes = mestranol.

[a] 12 weeks of active pills, 1 week of inert pills.

[b] 12 weeks of active pills, 1 week of EE only pills for withdrawal bleed.

Numbers in parentheses are the number of days at a particular dosage.

Modified from Wallach, 2000, with permission.

These oral contraceptives typically consist of a combination of an estrogen and a progestational agent taken daily for 3 weeks and then stopped for 1 week, during which time there is withdrawal uterine bleeding. Longer durations of active hormone administration, designed to minimize withdrawal bleeding, have been investigated (Edelman, 2006; Miller, 2003). Such extended-cycle products are now available: Seasonale and Seasonique (Barr Pharmaceuticals, Pomona, NY).

MECHANISMS OF ACTION

The contraceptive actions of COCs are multiple. The most important effect is to prevent ovulation by suppression of hypothalamic gonadotropin-releasing factors, which in turn prevents pituitary secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Estrogen suppresses FSH release and stabilizes the endometrium to prevent metrorrhagia, which is often called *breakthrough bleeding* in this setting. Progestins inhibit ovulation by suppressing LH, they thicken cervical mucus to retard sperm passage, and they render the endometrium unfavorable for implantation.

The net effect is extremely effective ovulation suppression, inhibition of sperm migration, and creation of an unfavorable endometrium for implantation. Thus, combined oral contraceptives, *if taken daily for 3 out of every 4 weeks,* provide virtually absolute protection against conception.

PHARMACOLOGY

In the United States, the only estrogens available are *ethinyl estradiol,* and less commonly its 3-methyl ether, *mestranol* . Almost all currently available *progestins* are 19-nortestosterone derivatives, but one is an aldosterone derivative. Although individual progestins were initially chosen because of their progestational potency, they are often compared and prescribed based on their presumed estrogenic, antiestrogenic, and especially their androgenic effects. Despite this, a scientific basis for such selective prescribing is lacking (Wallach, 2000). For example, all progestins lower serum free testosterone levels and inhibit 5α-reductase

and thus conversion of testosterone to the active dihydrotestosterone. Because of this, all progestins are expected to have salutary effects on androgen-related conditions such as acne (see Chap. 17, Acne).

DOSAGE

Since their initial development, COCs now contain markedly reduced amounts of estrogen and progestin. As a result, because most adverse effects are dose related, side effects have similarly decreased with modern pill dosages. For most, the lowest acceptable dose is governed by the ability to prevent unacceptable breakthrough bleeding. Although daily estrogen content varies from 20 to 50 μg of ethinyl estradiol, most pills contain 35 μg or less (see Table 5-3). The amount of progestin can be varied in two ways: (1) progestin dose remains constant during the cycleâ€”*monophasic* pills, and (2) progestinâ€”and in some, estrogenâ€”dosage varies during the cycleâ€”*biphasic* and *triphasic* pills.

Ideally, women should start COCs on the first day of a menstrual cycle, in which case an additional contraceptive method is unnecessary. A more traditional scheduleâ€”the *Sunday start* â€”requires pill initiation on the first Sunday following menstruation onset. This schedule necessitates use of an additional method for 1 week to ensure that conception does not occur. Alternatively, immediate initiation of COCs, regardless of menses, has been shown to be safe and to improve short-term continuation rates (Westhoff, 2007).

To obtain maximum protection and promote regular use, most suppliers offer dispensers that provide 21 sequential color-coded tablets containing hormones, followed by seven inert tablets of another color. It is important for maximum contraceptive efficacy that each woman adopt an effective scheme for assuring dailyâ€”or nightlyâ€—self-administration.

If one dose is missed, conception is unlikely with higher-dose monophasic estrogen and progestin pills. When this is recognized, a woman may choose to double that day's dose to minimize breakthrough bleeding. The remainder of the pill pack is completed with one pill taken daily.

If several doses are missed or lower-dose pills are used, the next dose is doubled and an effective barrier technique is added for the subsequent 7 days. The remainder of the pill pack is completed with one pill taken daily. Alternatively, a new pack can be started with a barrier method as additional contraception for a week. If withdrawal bleeding does not follow during the week of placebo pills, a woman should continue the pills but seek medical attention to exclude pregnancy.

PHASIC PILLS

These preparations were developed in an effort to reduce the amount of total progestin per cycle without sacrificing contraceptive efficacy or cycle control. The reduction is achieved by beginning with a low dose of progestin, and increasing it later in the contraceptive cycle. Theoretically, the lower total dose should result in a reduction in progestin-attributable metabolic changes and adverse side effects. The estrogen dose may be kept constant, or it also may be increased later in the cycle. In all such preparations, however, estrogens are kept between 20 and 40 μg of ethinyl estradiol (see Table 5-3).

Despite the cited advantages, both theoretical and actual, there are distinct disadvantages to triphasic formulations. These include confusion due to multicolored pills and breakthrough bleeding or spotting, which likely is increased compared with monophasic pills (Woods, 1992).

DRUG INTERACTIONS

Oral contraceptives interfere with the actions of some drugs (Table 5-4). Conversely, some drugs decrease the contraceptive effectiveness of COCs (Table 5-5). Phenytoin and rifampin are believed to increase breakthrough bleeding and reduce contraceptive effectiveness of pills containing less than 50 μg of ethinyl estradiol (Hatcher, 1998). Many antiretrovirals decrease contraceptive efficacy, therefore barrier contraceptive methods are recommended (University of California at San Francisco, 2005). Although package inserts for some broad-spectrum antibiotics such as ampicillin and tetracycline warn that they may reduce the efficacy of oral contraceptives, this likely is not true. Any decreased efficacy is related to underlying associated gastrointestinal symptoms, such as vomiting or diarrhea, which can decrease absorption. Another agent, vitamin C, competes for active sulfate in the intestinal wall and increases the bioavailability of ethinyl estradiol. Thus, erratic use of vitamin C can result in breakthrough bleeding (Kubba, 1993).

Table 5-4 Drugs Whose Effectiveness Is Influenced by Combination Oral Contraceptives

Interacting Drug	Documentation	Management
Analgesics		
Acetaminophen	Adequate	Larger doses of analgesic may be required
Aspirin	Probable	Larger doses of analgesic may be required
Meperidine	Suspected	Smaller doses of analgesic may be required
Morphine	Probable	Larger doses of analgesic may be required
Anticoagulants		
Dicumarol, warfarin	Controversial	
Antidepressants		
Imipramine	Suspected	Decrease dosage about a third
Tranquilizers		
Diazepam, alprazolam	Suspected	Decrease dose
Temazepam	Possible	May need to increase dose
Other benzodiazepines	Suspected	Observe for increased effect
Anti-inflammatories		
Corticosteroids	Adequate	Watch for potentiation of effects, decrease dose accordingly
Bronchodilators		
Aminophylline, theophylline, caffeine	Adequate	Reduce starting dose by a third
Antihypertensives		
Cyclopenthiazide	Adequate	Increase dose
Metoprolol	Suspected	May need to lower dose
Other		
Troleandomycin	Suspected liver damage	Avoid
Cyclosporine	Possible	May use smaller dose
Antiretrovirals	Variable	See manufacturer or other[a]

[a] University of California at San Francisco (UCSF): HIV Insite, 2005.

Modified from Wallach, 2000, with permission.

Table 5-5 Drugs that May Reduce Combined Hormonal Contraceptive Efficacy	
Interacting Drug	**Documentation**
Antituberculous	
Rifampin	Established; reduced efficacy if <50 μg EE
Antifungals	
Griseofulvin	Strongly suspected
Anticonvulsants and sedatives	
Phenytoin, mephenytoin, phenobarbital, primidone, carbamzepine, ethosuximide	Strongly suspected; reduced efficacy if <50 μg EE; trials lacking
Antibiotics	
Tetracycline, doxycycline	Two small studies find no association
Penicillins	No association documented
Ciprofloxacin	No effect on efficacy of a 30 μg EE + desogestrel pill
Ofloxacin	No effect on efficacy of a 30 μg EE + levonorgestrel pill
Antiretrovirals	Variable effects; see manufacturer or other[a]

EE = ethinyl estradiol.

[a] University of California at San Francisco (UCSF): HIV Insite, 2005.

Modified from Wallach, 2000, with permission

SAFETY

In general, oral contraceptives have proven to be safe for most women. The possibility of adverse effects from COCs has received so much attention for so long that clinicians as well as the public are frequently confused by the often conflicting reports.

BENEFICIAL EFFECTS

As shown in Table 5-6, there are many beneficial effects from use of the combined estrogen plus progestin contraceptives.

Table 5-6 Some Benefits of Combination Estrogen Plus Progestin Oral Contraceptives
Increased bone density
Reduced menstrual blood loss and anemia
Decreased risk of ectopic pregnancy
Improved dysmenorrhea from endometriosis
Fewer premenstrual complaints
Decreased risk of endometrial and ovarian cancer
Reduction in various benign breast diseases
Inhibition of hirsutism progression
Improvement of acne
Prevention of atherogenesis
Decreased incidence and severity of acute salpingitis
Decreased activity of rheumatoid arthritis

POSSIBLE ADVERSE EFFECTS

A number of metabolic changes, often qualitatively similar to those of pregnancy, have been identified in women taking oral contraceptives. For example, total plasma thyroxine and thyroid-binding proteins are elevated. Plasma cortisol concentration increases with a nearly comparable increase in transcortin. It is extremely important, therefore, that these pregnancy-like effects be considered when evaluating laboratory tests.

Lipids and Lipoproteins

In general, COCs increase serum triglyceride and total cholesterol levels. Estrogen decreases concentration of low-density lipoprotein (LDL) cholesterol and increases high-density lipoprotein (HDL) cholesterol. Some progestins cause the reverse (Stadel, 1981). The clinical consequences of these perturbations have almost certainly been overstated, and their impact on lipids is inconsequential for the vast majority of women (Wallach, 2000).

Carbohydrate Metabolism

Concern over deterioration in glucose tolerance, mediated principally by the progestin, is no longer warranted with current formulations (Speroff, 2001). In healthy women, large prospective studies with long-term surveillance demonstrate that COCs do not increase the risk of diabetes (Rimm, 1992). In fact, they do not increase the risk that women with a history of gestational diabetes will progress to overt diabetes (Kjos, 1998). Combination oral contraceptives may be used in women who have diabetes not complicated by associated vascular disease.

Protein Metabolism

Estrogens increase hepatic production of a variety of globulins. Increased angiotensinogen production appears to be dose related, and its conversion by renin to angiotensin I has been suspected to be associated with so-called *pill-induced hypertension* (Hypertension). Fibrinogen, and likely factors II, VII, IX, X, XII, and XIII, are increased in direct proportion to estrogen dose (Comp, 1996; Kaunitz, 1999). The relationship of these increased clotting factors to venous and arterial thrombosis is discussed in Hypertension, but the incidences of both forms of thrombosis appear to be estrogen-dose related (Mann, 1982).

Liver Disease

Cholestasis and *cholestatic jaundice* are uncommon complications of oral contraceptives. If they develop, signs and symptoms clear when the COCs are stopped. It appears that oral contraceptives may accelerate the development of gallbladder disease in women who are susceptible, but there is no overall increased long-term risk (Royal College of General Practitioners, 1982; Strom, 1986). There is no reason to withhold oral contraceptives from women who have recovered from viral hepatitis.

Neoplasia

A stimulatory effect on some cancers is always a concern with female sex steroids. Despite this, a number of studies indicate that it is unlikely that hormonal contraception causes cancer (Cancer and Steroid Hormone Study, 1986, 1987a, 1987b; Prentice, 1987; Schlesselman, 1988). In fact, a protective effect against ovarian and endometrial cancer was shown. There are, however, conflicting reports concerning the risks of premalignant and malignant changes of the liver, cervix, and breast.

Liver Cancer

Older contraceptives with larger estrogen doses were linked circumstantially with *hepatic focal nodular hyperplasia* and benign *hepatic adenoma* . Since that time, large studies of women taking contemporary low-dose oral contraceptives do not support such an association (Hannaford, 1997; Heinemann, 1998). Additionally, although an association between prolonged oral contraceptive use with *hepatocellular carcinoma* was reported by Neuberger and associates (1986), the large multicenter World Health Organization Study (1989) refutes this.

Cervical Cancer

There is a correlation between the risk of *cervical dysplasia* and oral contraceptive use, and the risk of *cervical cancer* increases after 5 years (Thomas, 1996; Vessey, 1983; Zondervan, 1996). It is unclear if these associations have a causal basis. For example, COC users are not protected from exposure to human papillomavirus unless they also use a barrier method. They also are more frequently screened cytologically for cervical cancer, and thus more likely to be diagnosed with dysplasia (Butterworth, 1992).

Breast Cancer

It is unclear whether oral contraceptives contribute to the development of *breast cancer* . In the largest study, no increased risk for breast cancer among COC users was noted (Cancer and Steroid Hormone Study, 1986). Moreover, risk did not vary according to specific preparations or duration of use. In addition, the Collaborative Group on Hormonal Factors in Breast Cancer (1996) re-analyzed data from 54 studies that included more than 53,000 women with breast cancer compared with over 100,000 controls. They found a small and significantly increased relative risk of breast cancer in current users of COCs. For women who had stopped use, relative risk was 1.16 at 1 to 4 years after stopping, and 1.07 at 5 to 9 years after stopping. The risk was not influenced by age at first use, duration of use, family history of breast cancer, first use prior to pregnancy, or the dose or type of hormone used. The lack of correlation with these factors calls into question the causal nature of the association. In this study, tumors associated with COC use tended to be less aggressive and to be detected at an earlier stage, a finding consistent with the possibility that the increased risk of breast cancer diagnosis was due to greater surveillance among users. In a recent case-control studyâ€"4,575 cases and 4,682 controlsâ€"there was no relationship between either current or past COC use and breast cancer (Marchbanks, 2002).

Current data neither support nor refute an association between COCs and ovarian or breast cancer among women heterozygous for *BRCA1* and *BRCA2* genes. The risks of unplanned pregnancy need to be considered along with those of any method of contraception (Grenader, 2005; McGuire, 2004; Milne, 2005). As a corollary, COC use for ovarian cancer *prevention* in these women is not currently advised (Modan, 2001).

Nutrition

Changes in serum levels of several nutrients, similar to those induced by normal pregnancy, have been described for women who use oral contraceptives. Lower plasma levels are reported for ascorbic and folic acid, vitamin B_6 (pyridoxine) and vitamin B_{12} , niacin, riboflavin, and zinc. An adequate diet is sufficient prophylaxis against any detrimental deficiency (Mooij, 1991).

Cardiovascular Effects

There are a number of infrequent but significant cardiovascular risks associated with hormonal contraceptive use.

Thrombosis and Embolism

The risk of *deep vein thrombosis* and *pulmonary embolism* is increased in women who use oral contraceptives (Realini, 1985; Stadel, 1981). This risk appears increased with transdermal patch use compared with COC use (Cole, 2007). These risks clearly are estrogen-dose related, and are decreased with formulations containing 20 to 35 µg of ethinyl estradiol (Westhoff, 1998). In an evidence-based review of six studies, Mishell and associates (2000) estimated the risks of venous thromboembolism in COC users. They concluded that the risk is increased three- to fourfold in current usersâ€"but not former users. The general population risk is lowâ€"about 1 per 10,000 woman-yearsâ€"and thus the incidence with COCs of 3.0 to 4.0 per 10,000 woman years is still low. Importantly, the risk is clearly lower than the incidence of 5.7 per 10,000 woman years estimated for pregnancy.

The enhanced risk of thromboembolism appears to decrease rapidly once COCs are stopped. Women who develop thromboembolism while taking estrogen-containing contraceptives, however, also appear to be at increased risk during pregnancy and postpartum. Those most at risk for venous thrombosis and embolism include women with some of the thrombophiliasâ€"for example, protein C or S deficiencies or factor V Leiden mutation (Comp, 1996; Mohllajee, 2006, van Vlijmen, 2007). Other clinical factors that increase the risk of venous thrombosis and embolism are hypertension, obesity, diabetes, smoking, and a sedentary lifestyle (Hatcher, 2004).

The little evidence of an increased risk of *perioperative thromboembolism* and oral contraceptives is based on older, high-estrogen preparations. There are no studies of low-dose formulations, and any decision to stop their use prior to surgery should be made individually.

Stroke

According to the World Health Organization Collaborative Study (1998), *ischemic* and *hemorrhagic strokes* are uncommon in nonsmoking women younger than 35 years. Their incidence is 10 and 24 events per 1 million woman years, respectively. The earlier reports by Lidegaard (1993, 1998) of an increased risk of stroke in women using low-dose estrogen contraceptives stimulated a number of focused studies. At least five subsequent studies concluded that COC use by healthy, nonsmoking women is not associated with an increased risk of stroke (Petitti, 1996; World Health Organization Collaborative Study, 1996). In two of these studies, women who took COCs were at a higher risk of stroke if they had hypertension, were smokers, or had migraine headaches (Mishell, 2000; Schwartz, 1998).

Women taking COCs who have *migraine headaches with aura* have a two- to fourfold increased risk of stroke compared with nonusers (Curtis, 2002). This finding led the World Health Organization (WHO) to change the Medical Eligibility Criteria to exclude women with migraines from taking COCs. It seems wise to also preclude women who have *migraine headaches without aura* from taking these combination contraceptives. A progestin-only pill, barrier methods, or an IUD is more appropriate (World Health Organization, 2004).

Hypertension

An association between COCs and *hypertension* was apparent by the late 1960s. Earlier higher-dose contraceptives, presumably in response to estrogen, increased plasma angiotensinogen in most women, although only a few became hypertensive. Current low-dose formulations increase the absolute risk of clinically significant hypertension only slightly (Chasan-Taber, 1996). The development of gestational hypertension, including preeclampsia, does not preclude subsequent COC use. That said, women who currently have hypertension need to be thoroughly evaluated (Curtis, 2002). The American College of Obstetricians and Gynecologists (2005b) recommend control of hypertension before COC use is considered.

Myocardial Infarction

Low-dose oral contraceptives are not associated with an increased risk of *myocardial infarction* in women who are nonsmokers (Mishell, 2000; Petitti, 1998; Sidney, 1996, 1998; World Health Organization Collaborative Study, 1997). In fact, the American College of Obstetricians and Gynecologists (2000b) states there is no contraindication to oral contraceptives in nonsmoking women older than 35 years. Also, the Food and Drug Administration (FDA) revised labeling of oral contraceptives to remove restrictions for nonsmoking women older than 40. It is important to recognize that smoking is an independent risk factor for myocardial infarction,

and that smoking and oral contraceptives act synergistically to increase this risk, especially beyond age 35.

Effects on Reproduction

Postpill amenorrhea after combination hormonal contraception discontinuation likely reflects a pre-existing problem (Wallach, 2000). At least 90 percent of women who previously ovulated regularly will do so within 3 months after discontinuance of oral contraceptives.

There is no evidence that COCs are teratogenic with the exception of sex organ development (Briggs, 2002). Women should be counseled regarding these findings. Many discontinue their pills because of teratogenicity fears when menses are late, and they then become pregnant.

Lactation

There are limited data on the interaction of COCs and lactation. Minute quantities of the hormones are excreted in the breast milk, but no adverse effects on infants have been noted. There is concern that these agents reduce the volume of breast milk, although a Cochrane Review confirmed the ambiguity of these data (Truitt, 2003). Because progestin-only oral contraceptives have little effect on lactation, they are preferred for up to 6 months in women who are exclusively breast feeding (Oral Progestins). Those who are only intermittently breast feeding should use effective contraception beginning as soon as 3 weeks postpartum (Kaunitz, 1997). According to guidelines published by the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2002) "nursing mothers may begin using oral contraceptives as soon as their milk supply is established".

Weight Gain

There have been a few retrospective studies that have reported conflicting results regarding COCs efficacy and body weight (Brunner, 2005; Holt, 2002, 2005). To address this, Gallo and associates (2004, 2006) reviewed 42 randomized trials and the Cochrane Database. They concluded that available evidence was insufficient to determine effects of COCs on weight, but that no large effect was evident.

Other Effects

Cervical mucorrhea, likely due to cervical eversion, is fairly common in response to the estrogen component (Critchlow, 1995). The mucus at times may be irritating to the vagina and vulva. *Vaginitis* or *vulvovaginitis,* especially that caused by *Candida* species, also may develop.

Hyperpigmentation of the face and foreheadâ€"also known as *chloasma* â€"is more likely in women who demonstrated such a change during pregnancy. This is seen much less commonly with the use of low-dose estrogen formulations. As discussed, oral contraceptives may improve acne.

Uterine *leiomyomas* do not increase in size with oral contraceptive use (Wise, 2004). Low-dose estrogen formulations are not associated with *depression* , and indeed, may cause it to improve (Goldzeiher, 1995).

Multiple studies have been conducted to evaluate the relationship between the use of oral and injectable contraceptives and the risk of *HIV infection.* Although most of these have methodologic limitations, on balance they do not suggest increased risk (Stephenson, 1998). On the other hand, hormonal contraception does not *prevent* the transmission of HIV infection or any other viral infection. Consistent use of condoms for the prevention of sexually transmitted infections should be emphasized.

RISK OF DEATH

Mortality associated with oral contraceptives is rare if a woman is younger than 35, has no systemic illness, and does not smoke (see Table 5-1). Porter and associates (1987) reported only one death attributed to oral contraceptive use in nearly 55,000 woman-years from the Group Health Cooperative of Puget Sound.

POSTPARTUM USE

Women who do not breast feed may ovulate before 6 weeks after pregnancy. They do so much earlier after an early pregnancy loss or induced abortion (see Chap. 6, Resumption of Ovulation Following Miscarriage). There is an advantage, therefore, to starting oral contraceptives before the traditional 6-week postpartum examination. On the other hand, increased risks of adverse effects,

especially venous thromboembolism, might be anticipated from use of estrogen-progestin contraceptives earlier in the puerperium. The use of 35 µg or lower estrogen doses has reduced this risk greatly. Thus far, in our now extensive experience in which oral contraceptives have been started during the third week postpartum, there has been no evidence of increased morbidity or mortality.

CONTRAINDICATIONS

It could be argued that because pregnancy is usually more dangerous than oral contraception, that no contraindication to oral contraceptives should be considered absolute. Pragmatically, considering the multiplicity of alternate contraceptive methods, if a contraindication listed in Table 5-7 is present, combined COCs should probably not be prescribed, and alternative methods should be encouraged.

Table 5-7 Typical Package Insert Listing Contraindications and a Warning About the Use of Combination Oral Contraceptives

Contraindications: Combination contraceptives should not be used in women with:
Thrombophlebitis or thromboembolic disorders
History of deep vein thrombophlebitis or thrombotic disorders
Cerebrovascular or coronary artery disease
Thrombogenic cardiac valvulopathies
Thrombogenic heart arrhythmias
Diabetes with vascular involvement
Severe hypertension
Known or suspected breast carcinoma
Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia
Undiagnosed abnormal genital bleeding
Cholestatic jaundice of pregnancy or jaundice with pill use
Hepatic adenomas or carcinomas or active liver disease with abnormal liver function
Known or suspected pregnancy
Major surgery with prolonged immobilization
Warning
Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with the extent of smoking (in epidemiologic studies, 15 or more cigarettes per day was associated with a significantly increased risk), and is marked in women older than 35 years. Women who use oral contraceptives should be strongly advised not to smoke.

From Physicians Desk Reference, 2006, with permission.

That said, we must remember that most of the lists that proscribe COC use in women with chronic illnesses were arrived at intuitively and without data. An example is the use of highly effective low-dose COCs in women with systemic lupus erythematosus. While considered a contraindication to COC use, two recent randomized trials of over 300 women with lupus showed no increased adverse effects of COCs compared with placebo (Petri, 2005; SÃ¡nchez-Guerrero, 2005).

TRANSDERMAL ADMINISTRATION

The combined contraceptive approved patch (Ortho Evra, Ortho-McNeil Pharmaceutical, Raritan, NJ) is applied to the buttocks,

upper outer arm, lower abdomen, or upper torso but avoiding the breasts (Fig. 5-2). It delivers 150 µg of the progestin, norelgestromin, and 20 µg of ethinyl estradiol daily. A new patch is applied each week for 3 weeks, followed by a patch-free week to allow for withdrawal bleeding.

FIGURE 5-2

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Ortho Evra, an estrogen-progestin transdermal contraceptive patch. *(Courtesy of Ortho-McNeil Pharmaceutical.)*

In a randomized trial by Audet and co-workers (2001), the patch was slightly more effective than a low-dose oral contraceptive in preventing pregnancyâ€”1.2 versus 2.2 pregnancies per 100 woman-years. Although overall well tolerated and safe, dysmenorrhea and breast tenderness were more frequent in the patch group, as was breakthrough bleeding in the first two cycles. Almost 5 percent of the patches required replacement for either complete (1.8 percent) or partial detachment (2.8 percent). In about 3 percent of women, the patch caused an application site reaction severe enough to limit continued use.

Pooled data suggest that women who weigh 90 kg or more are at increased risk for contraceptive failure. Of 15 failures reported, five women met this threshold, even though they constituted less than 3 percent of the study population (Zieman, 2002). This translates to a relative risk of failure of 16 or more.

The patch, therefore, is an effective alternative hormonal contraceptive method for women who prefer weekly application rather than daily dosing and who find a transdermal method acceptable. Its metabolic and physiologic effects should be substantively the same as with low-dose oral contraceptives, although accumulated experience is limited.

TRANSVAGINAL ADMINISTRATION

An intravaginal hormonal contraceptive ringâ€”*NuvaRing* (Organon, Roseland, NJ)â€”is a flexible polymer ring with an outer diameter of 54 mm and an inner diameter of 50 mm (Fig. 5-3). Its core contains ethinyl estradiol and the progestin, etonogestrel, which are released at rates of 15 µg and 120 µg per day, respectively. Although this results in serum hormone levels lower than comparable low-dose oral contraceptives, ovulation inhibition is complete (Mulders, 2001). It is highly effective, and in one study, the failure rate was 0.65 per 100 woman-years (Roumen, 2001).

FIGURE 5-3

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

NuvaRing, an estrogen-progestinâ€“releasing vaginal contraceptive ring. *(Courtesy of Organon.)*

The rings are refrigerated, and once dispensed their shelf life is 4 months (Burkman, 2002). The ring is initially placed within 5 days of the onset of menses. It is removed after 3 weeks of use for 1 week to allow withdrawal bleeding. After this, a new ring is inserted. Breakthrough bleeding is uncommon.

Almost 20 percent of women and 35 percent of men reported being able to feel the ring during intercourse. If this is bothersome, the ring may be removed for coitus, but should be replaced within 3 hours.

INTRAMUSCULAR ADMINISTRATION

There is only one combination preparation for intramuscular injection. Previously marketed in the U.S. as *Lunelle,* this contraceptive contains 25 mg of medroxyprogesterone acetate plus 5 mg of estradiol cypionate. One injection is given monthly. The drug inhibits ovulation and suppresses endometrial proliferation (Aedo, 1985). Serum estradiol values reach a peak level by 3 to 4 days postinjection and then decline, leading to withdrawal bleeding 20 to 25 days after injection (Garceau, 2000).

Only six method failures in 70,000 woman-years of use have been reported (Hall, 1994). This degree of effectiveness compares similarly with that seen following female sterilization procedures. Contraindications are similar to those for COCs as shown in Table 5-7.

In 2002, prefilled Lunelle syringes were recalled by the manufacturer due to lack of assurance of full contraceptive potency. Although still FDA-approved, this method has not since been marketed in the United States.

Progestational Contraceptives

ORAL PROGESTINS

Progestin-only pills, also known as *mini-pills,* are taken daily. Unlike COCs, they do not reliably inhibit ovulation. Rather, their effectiveness depends more on cervical mucus alterations and effects on the endometrium. Because the mucus changes do not persist beyond 24 hours, to be maximally effective it should be taken at the same time every day.

These contraceptives have not achieved widespread popularity because of a much higher incidence of irregular bleeding and a

slightly higher pregnancy rate than combination contraceptives (see Table 5-2). Improved effectiveness has been reported for married, and in a progressive fashion, older women (Guillebaud, 1985).

Benefits

Progestin-only pills have minimal if any effect on carbohydrate metabolism or coagulation, and they do not cause or exacerbate hypertension. They may be ideal for some women who are at increased risk of cardiovascular complications. This includes women with a history of thrombosis, hypertension, or migraine headaches, or who are older than 35 years and smoke. In addition, the mini-pill is often an excellent choice for lactating women. In combination with breast feeding, it is virtually 100-percent effective for up to 6 months and does not impair milk production (Betrabet, 1987; Shikary, 1987).

Disadvantages

The major drawback of progestin-only pills is contraceptive failure. With these failures, there is a relative increase in the proportion of ectopic pregnancies (Sivin, 1991). Irregular uterine bleeding is another distinct disadvantage and may manifest as amenorrhea, metrorrhagia, or prolonged periods of menorrhagia. Functional ovarian cysts develop with a greater frequency in women using these agents, although they do not usually necessitate intervention.

As discussed, one distinct disadvantage is that these contraceptives must be taken at the same or nearly the same time each day. **If a progestin-only pill is taken even 4 hours late, an additional form of contraception must be used for the next 48 hours.** Their effectiveness is decreased by medications that include anticonvulsantsâ€”phenytoin, carbamazepine, felbamate, oxcarbazepine, primidone, and topiramate; and antituberculous agentsâ€”rifampicin and rifabutin (Speroff, 2001). Women taking any of these medications should not use this form of contraception. Finally, unlike combined oral contraceptives, the mini-pill does not improve acne, and may even worsen it in some women.

Contraindications

Progestin-only pills, like other methods of contraception, are contraindicated in women with unexplained uterine bleeding or breast cancer.

INJECTABLE PROGESTIN CONTRACEPTIVES

Depot medroxyprogesterone acetate (*Depo-Provera,* Pfizer, New York, NY) and norethindrone ethanthate (*Norgest*) have been used effectively worldwide for many years. Depo-Provera, although available for many years before, was approved in 1992 for contraceptive use in the United States. Norgest is not yet available. Their mechanisms of action are similar to those for oral agents: ovulation inhibition, increased cervical mucus viscosity, and stimulation of an endometrium unfavorable for ovum implantation (Mishell, 1996).

Depot medroxyprogesterone is injected deeply into the upper outer quadrant of the buttock or into the deltoid muscles without massage to ensure that the drug is released slowly. The usual dose is 150 mg every 90 days. An additional contraceptive method should be used for at least 2 weeks after the initial injection.

Recently, *depo-subQ provera 104* has become available. It contains 104 mg of medroxyprogesterone acetate that is injected subcutaneously every 90 days. In three clinical studies, no pregnancies were detected among 2,042 women using it for up to 1 year.

Benefits and Disadvantages

Injected progestins have contraceptive effectiveness comparable with or better than COCs, a long duration of action, and minimal to no impairment of lactation (American College of Obstetricians and Gynecologists, 2000a). Iron-deficiency anemia is less likely in long-term users, probably as a result of amenorrhea, which develops in 80 percent of women after 5 years (Gardner, 1970).

The principal disadvantages of depot progestins include irregular menstrual bleeding and prolonged anovulation after discontinuation resulting in delayed fertility resumption. Cromer and associates (1994) reported that a fourth of women discontinued its use in the first year because of irregular bleeding. After the injections are stopped, a fourth of women will not resume regular menses for up to a year (Gardner, 1970).

The reported risks of breast cancer are conflicting. Skegg and colleagues (1995) pooled the results of the New Zealand and WHO case-control studies. These studies included almost 1,800 women with breast cancer and 14,000 controls. Within the first 5 years of use, the contraceptive was associated with a twofold risk of cancer, but overall the risk was not increased. Cervical and hepatic malignancies do not appear to be increased, and the risk of ovarian and endometrial cancers is decreased (Earl, 1994; Kaunitz, 1996). The risk of cervical carcinoma in situ may be increased (Thomas, 1995).

Although weight gain is often attributed to depot medroxyprogesterone, conclusive evidence is lacking (Mainwaring, 1995; Moore, 1995; Taneepanichskul, 1998). Breast tenderness is reported by some users, as is depression, although a causal link for the latter has not been demonstrated.

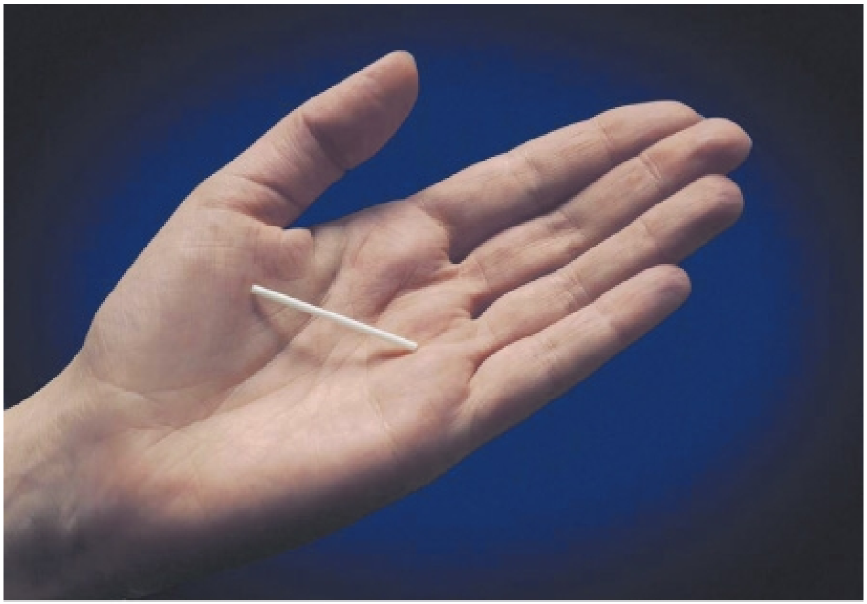
One concern in long-term users of both intramuscular and subcutaneous depot medroxyprogesterone is loss of bone mineral density (Scholes, 1999). It is probably most relevant for teenagers because bone density increases most rapidly from age 10 to 30 (Cromer, 1996; Sulak, 1999). Reassuringly, bone loss appears to be reversible after discontinuation of the drug (Cundy, 1994). The addition of a "black box" warning to clinicians for these two injectable progestins has been added and explains that they should be used for longer than 2 years only if other methods of birth control are inadequate.

PROGESTIN IMPLANTS

In these systems, a progestin is delivered by a subdermally implanted device containing the drug and coated with a compound to prevent fibrosis. Currently, there are two preparations. The *Norplant System* (Wyeth, Madison, NJ) contains levonorgestrel in six silastic containers. Its contraceptive effectiveness persists for 60 months, at which point the system should be removed (Hatcher, 1998). Despite its effectiveness, safety, and patient satisfaction, use of this excellent contraceptive waned dramatically following law suits involving this method. Allegations of illness related to the silicone-based rods created a climate of litigation around this system, and currently it is no longer available. A fund has been established by the manufacturer to ensure medical access for removal.

The *Implanon System* (Organon, Roseland, NJ) is a single rod subdermal implant with 68 mg of the progestin, etonogestrel, and has an ethylene vinyl acetate co-polymer cover (Fig. 5-4). Similar to the Norplant System, daily release of etonogestrel causes ovulation suppression, cervical mucus thickening, and an atrophic endometrium.

FIGURE 5-4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Implanon system rod. *(Courtesy of Organon.)*

EMERGENCY CONTRACEPTION

Many women present for contraceptive care following consensual but unprotected sexual intercourse, and in some cases aggravated sexual assault. In these situations, there are a number of methods that if used correctly, will substantially decrease the likelihood of an unwanted pregnancy.

Hormonal Emergency Contraception

This is also known as the *morning after pill,* or the *Yuzpe method.* There are two hormonal methods currently available. The Yuzpe method consists of commonly available COCs, and the other is a progestin-only productâ€"*Plan B* (Barr Pharmaceuticals, Pomona, NY). A third product, consisting of an estrogen and progestin combinationâ€"*Preven,* was approved by the FDA in 1998, but withdrawn from the market in 2004.

Access to emergency contraception has not been universal. Trussell and colleagues (2000) found that only 75 percent of attempts to access care through the Emergency Contraception Hotline were successful. Clinicians can register to be included as a resource and women can obtain referrals on the Hotline at 1-888-NOT-2-LATE (888-668-2528), the Emergency Contraception Website (http://www.not-2-late.com), or Pastillas Anticonceptivas de Emergencia (http://www.en3dias.org.mx).

ESTROGEN-PROGESTIN COMBINATIONS

A number of combined oral contraceptive regimens were approved in 1997 by the FDA for use as emergency contraception (Table 5-8). Tablets are taken within 72 hours of intercourse, followed 12 hours later by a second dose. Regimens are more effective the sooner they are taken after unprotected sex.

Table 5-8 Prescriptive Equivalents of Dedicated Products and Common Oral Contraceptives for Use as Emergency Contraception

Trade Name	Formulation	Pills per Dose[a]
Dedicated products		
Plan B	0.75 mg levonorgestrel	1
Preven	0.05 mg ethinyl estradiol 0.25 mg levonorgestrel	2
Oral contraceptives		
Ovrette	0.075 mg norgestrel	20
Ogestrel, Ovral	0.05 mg ethinyl estradiol + 0.5 mg norgestrel	2
Low-Ogestrel, Lo/Ovral, Nordette, Levlen, Levora	0.03 mg ethinyl estradiol 0.3 mg norgestrel	4
TriLevlen (yellow), Triphasil (yellow), Trivora (pink)	0.03 mg ethinyl estradiol 0.125 mg levonorgestrel	4
Alesse, Levlite	0.02 mg ethinyl estradiol 0.1 mg levonorgestrel	5

[a] Treatment consists of two doses taken 12 hours apart. Use of an antiemetic agent before taking the medication will lessen the risk of nausea, which is a common side effect.

From American College of Obstetricians and Gynecologists, 2005a, with permission.

Emergency hormone contraceptive regimens are highly effective and decrease the risk of pregnancy by up to 94 percent (American College of Obstetricians and Gynecologists, 2005a). Thus, if 100 women had unprotected intercourse during the second to third

week of their menstrual cycle, eight would be expected to conceive. With appropriate use of one of these regimens, only two would actually conceive.

Nausea and vomiting are major problems due to high-dose estrogen in these regimens. Trussell and associates (1998a) reported nausea in 50 percent of women and vomiting in 20 percent. For this reason, we routinely prescribe an oral antiemetic at least 1 hour before each dose. Raymond and colleagues (2000) conducted a randomized trial and found that 1-hour pretreatment with 50-mg meclizine given orally decreased nausea substantially. Ragan and associates (2003) found that 10 mg of oral metoclopramide decreased both nausea and cramping compared with placebo. If a woman vomits within 2 hours of a dose, the dose must be repeated.

PROGESTINS ONLY

Plan B consists of two tablets each containing 0.75 mg levonorgestrel. The first dose is taken within 72 hours of unprotected coitus and the second dose 12 hours later (see Table 5-8). According to the Task Force on Postovulatory Methods of Fertility Regulation (1998), mini-pill progestins are more effective than combination estrogen-progestin pills. This regimen resulted in a crude pregnancy rate of 1.1 compared with 3.2 percent in a similar group of women treated with the Yuzpe regimen. Moreover, Ellertson and colleagues (2003) reported a 55-percent pregnancy prevention rate if Plan B was taken as late as 4 to 5 days after unprotected intercourse.

In 2006, the FDA approved Plan B as an over-the-counter option for women aged 18 years and older (U. S. Food and Drug Administration, 2006). As a result, in nine states, women older than 18 may now obtain Plan B without a prescription. These include Alaska, California, Hawaii, Maine, Massachusetts, New Hampshire, New Mexico, Washington and Vermont.

MECHANISM OF ACTION

The major mechanism of action is inhibition or delay of ovulation (U.S. Food and Drug Administration, 1997). Other suggested mechanisms include alteration of the endometrium to prevent implantation, sperm penetration, and tubal motility (American College of Obstetricians and Gynecologists, 2005a). **Established pregnancies are not harmed.** When evaluated in animals, emergency contraception does not prevent ovulation or implantation (Croxatto, 2003; Marions, 2004).

Copper-Containing Intrauterine Devices

Fasoli and co-workers (1989) summarized nine studies that included results from 879 women who accepted some type of copper-containing intrauterine device (IUD) as a sole method of postcoital contraception. The only pregnancy reported aborted spontaneously. Trussell and Stewart (1998) reported that when an IUD was inserted up to 5 days after unprotected coitus, the failure rate was 1 percent. A secondary advantage is that this method also puts in place an effective 10-year method of contraception.

Mifepristone (RU 486) and Epostane

These medications are discussed in Chapter 6, Medical Abortion. They should be ideal for postcoital contraception, either by blocking progesterone production (epostane), or interfering with its action (mifepristone). Implantation prevented by either mechanism results in so-called *menstrual induction.*

Ashok and colleagues (2002) reported that a single 100-mg tablet of mifepristone was more effective than the Yuzpe regimen with crude pregnancy rates of 0.6 versus 3.6 percent, respectively. There were also fewer side effects with mifepristone. Although hormonal regimens must be used within 72 hours of unprotected intercourse, mifepristone is effective up to 17 days after intercourse (Weiss, 1993).

Failure of Emergency Contraception

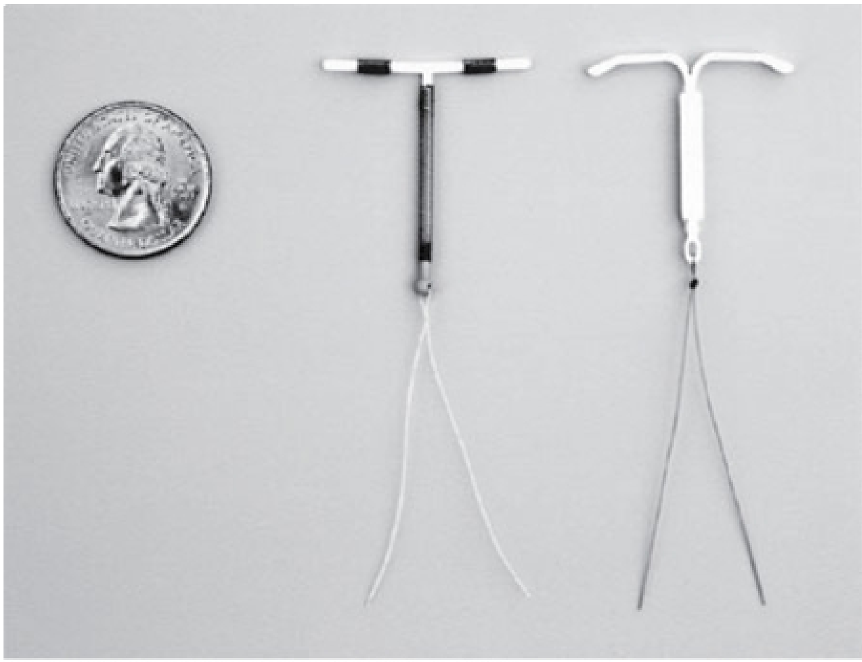
If menstruation is delayed for more than 3 weeks past its expected onset, pregnancy is likely. Any postcoital contraceptive method is associated with failures, which likely can be reduced by employing a barrier technique until the next menses to prevent fertilization after use of the postcoital method.

MECHANICAL METHODS OF CONTRACEPTION

Intrauterine Contraceptive Device

At one time in the United States, approximately 7 percent of sexually active women used an intrauterine device (IUD) for contraception. The two devices currently approved for use in this country are shown in Fig. 5-5. Unwanted pregnancies during the first year of perfect use are 0.6 percent for the copper-containing *ParaGard T 380A* (Duramed Pharmaceuticals, Pomona, NY) and 0.1 percent for the levonorgestrel-containing *Mirena* (Bayer HealthCare Pharmaceuticals, Wayne, NJ). Respective typical failure rates are 0.8 percent and 0.1 percent.

FIGURE 5-5



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Intrauterine contraceptive devices available in 2006: copper-containing ParaGard T 380A (**left**) and levonogestrel-releasing Mirena (**right**). *(Courtesy of Duramed Pharmaceuticals, Raritan, NJ, and Bayer HealthCare Pharmaceuticals, Montvale, NJ).*

With new information on safety, the IUD is once again gaining in popularity for several reasons:

1. Both ParaGard and Mirena are "use and forget" effective reversible contraceptive methods that do not have to be replaced for 10 and 5 years, respectively.
2. It is now better established that the major actions of IUDs are contraceptive and not abortifacient.
3. The risk of pelvic infections is markedly reduced with the currently used monofilament string along with techniques to ensure safer insertion.
4. The risk of an associated ectopic pregnancy has been clarified, to show that the contraceptive effect decreases the absolute number of ectopic pregnancies by half, compared with women not using contraception (World Health Organization, 1985, 1987). That said, with contraceptive failure, pregnancy is still more likely to be ectopic (Furlong, 2002).
5. Legal liability appears to be lessened because the FDA currently classifies available devices as drugs (Mishell, 1997). As such, manufacturers must provide product information to be read by women prior to insertion. Signed consent forms that include a reasonable listing of risks and benefits are also required.

TYPES OF DEVICES

Those that are *chemically inert* are composed of a nonabsorbable material, most often polyethylene, and impregnated with barium

sulfate for radiopacity. *Chemically active* devices have continuous elution of copper or a progestational agent. At the present time, only chemically active IUDs are available.

Levonorgestrel-Containing Intrauterine Device

The Mirena device releases levonorgestrel into the uterus at a relatively constant rate of 20 μg/d, which reduces the systemic effects of the progestin. It is a T-shaped polyethylene structure that has its stem wrapped with a cylinder made of polydimethylsiloxane and levonorgestrel. A permeable membrane surrounds the mixture to regulate the rate of hormone release. A monofilament brown polyethylene thread is attached to a small loop at the distal end of the device's vertical body.

Copper-Containing Intrauterine Device

The ParaGard T 380A device is composed of polyethylene with barium sulfate. The stem is wound with 314 mm^2 of fine copper wire, and the arms each have 33-mm^2 copper bracelets; these total 380 mm^2 of copper. Two strings extend from the base of the stem (see Fig. 5-5). Originally blue, the strings now are white.

MECHANISMS OF ACTION

These have not been defined precisely and are the subject of ongoing controversy. Interference with successful implantation of the fertilized ovum, which at one time was believed to be the main mode of action, is less important than prevention of fertilization (Mishell, 1997; Stanford, 2002). The intense local inflammatory response induced in the uterus, especially by copper-containing devices, leads to lysosomal activation and other inflammatory actions that are spermicidal (Alvarez, 1988; Ortiz, 1987). In the unlikely event that fertilization does occur, the same inflammatory actions are directed against a blastocyst. And finally, the endometrium is transformed into a hostile site for implantation.

In long-time progestin device users, the endometrium becomes atrophic. There may be a major effect in preventing fertilization by spermicidal action, or speeding ovum transport through the fallopian tube, or both (Alvarez, 1988; Ortiz, 1987). The progestin may interfere with sperm penetration through thickened cervical mucus, and it inhibits ovulation, but not consistently (Nilsson, 1984).

EFFECTIVENESS

One-year continuation rates are equal to those of oral contraceptives. This almost certainly is due to the effectiveness of IUDs and a once-only approach to contraception. Their effectiveness is similar overall to that of tubal sterilization (American College of Obstetricians and Gynecologists, 2003a). Importantly, the unintended pregnancy rate decreases progressively after the first year of use. The levonorgestrel-containing Mirena device has a typical user failure rate of 0.1 percent, which is lower than the copper-containing ParaGard (Rowe, 1992).

OTHER BENEFICIAL EFFECTS

The Mirena device reduces menstrual blood loss and can even be used to treat menorrhagia (see Chap. 8, Levonorgestrel-Containing Intrauterine System) (American College of Obstetricians and Gynecologists, 2006). Moreover, reduced blood loss is often associated with a reduction in dysmenorrhea. Despite their higher up-front costs, the overall extended use of IUDs makes their long-term cost effectiveness competitive with other forms of contraception. Women with contraindications to COCs can often use these devices. The device is also reported to reduce the incidence of pelvic infections (Toivonen, 1991; van den Hurk, 1999).

ADVERSE EFFECTS

Numerous complications have been described with use of various intrauterine devices. For the most part, however, common side effects with these two devices have not been serious, and serious side effects have not been common. Moreover, with extended use and advancing user age, unintended pregnancy, expulsion, and bleeding complications decrease in frequency.

Uterine Perforation

The earliest adverse effects are those associated with insertion. They include clinically apparent or silent *uterine perforation,* which occurs while sounding the uterus or during insertion. Perforations occur at a rate of approximately 1 per 1,000 insertions (World Health Organization, 1987). Although devices may migrate spontaneously into and through the uterine wall, most perforations occur, or at least begin, at the time of insertion.

Cramping and Bleeding

It is common for women to have uterine cramps and some bleeding soon after IUD insertion. These persist for a variable time. Cramping can be minimized by administering a nonsteroidal anti-inflammatory agent approximately 1 hour prior to insertion. Any associated increase in menstrual cramping may also be treated with these drugs.

Menorrhagia

Menstrual blood loss is commonly doubled with use of the ParaGard device (see Chap. 8, Copper-Containing Intrauterine Device). Because this may cause iron-deficiency anemia, iron salts are given prophylactically and most providers perform hemograms annually. Menorrhagia is a troubling side effect, and approximately 10 to 15 percent of women using the copper device have it removed for this problem (Hatcher, 1998). In contrast, the Mirena device is associated with progressive amenorrhea, which is reported by 30 percent of women after 2 years and by 60 percent after 12 years (Ronnerdag, 1999).

Infection

A variety of *pelvic infections,* in some cases fatal, have been described with intrauterine devices. These include *septic abortion,* which mandates immediate curettage. *Tubo-ovarian abscesses* â€”sometimes unilateralâ€”have been described. With suspected infection, antimicrobial treatment is given. There is mixed evidence with upper genital tract infection whether the IUD should be removed after therapy has been initiated (Grimes, 2000).

Historically, there has been much debate regarding appropriate candidates for IUD use. For example, its use was discouraged for women under the age of 25 or those of low parity. Recent well-designed studies indicate that sexual behavior and sexually transmitted disease history are the important risk factors. The FDA has correspondingly made changes to the package insert so that no longer are the restrictions based on sexual behavior aloneâ€”appropriate counseling and candidate selection are most important. Thus, nulliparous and multiparous women in mutually monogamous relationships may safely use the IUD (Speroff, 2001).

The major risk of infection is at the time of insertion and does not increase with long-term use. There is also a small increased risk of pelvic infection for up to the first 20 days (Farley, 1992). There currently is no evidence that prophylactic antibiotic administration at the time of IUD insertion reduces the risk of infection in women at low risk for sexually transmitted infections (American College of Obstetricians and Gynecologists, 2001; Sinei, 1990; Walsh, 1998). With long-term use of current devices, pelvic infection rates are comparable to those in oral contraceptive users. Any infection after 45 to 60 days should be considered sexually transmitted and appropriately treated (see Chap. 3, Treatment).

Fiorino (1996) cited an incidence of 7 percent of *Actinomyces* species seen on cytology smears from women using IUDs compared with less than 1 percent in nonusers. In some cases, pelvic inflammatory disease may develop (Dunn, 2006). Women who developed a pelvic abscess caused by this organism had used the device for a mean of 8 years before symptoms were noted. In the absence of symptoms, the incidental finding of *Actinomyces* by cytology has uncertain significance. The American College of Obstetricians and Gynecologists (2005c) reviewed treatment options, which include expectant management, an extended course of antibiotics, IUD removal, and antibiotics plus IUD removal. It was concluded that if symptomatic infection develops in women who harbor *Actinomyces,* then the IUD should be removed and antibiotic therapy given.

Pregnancy with Retained IUD

Early identification of pregnancy is important in these women. Up to about 14 weeks, the tail of the device may be visible through the cervix. If seen, it should be removed. This will reduce subsequent complications if the woman chooses to continue the pregnancy. For example, Tatum and co-workers (1976) reported the miscarriage rate to be 54 percent with the device left in situ compared with 25 percent if promptly removed. Second-trimester miscarriages with an IUD in place are more likely to be septic than those without an IUD (Lewit, 1970; Vessey, 1974). Sepsis may be fulminant and often fatal. With the device left in, the frequency of low birthweight, chiefly from preterm delivery, was 20 percent, compared with about 5 percent with removal. Fetal malformations have not been reported to be increased with a device in place (Vessey, 1979).

If the tail is not visible, attempts to locate and remove the device may result in pregnancy loss. Some have successfully used sonography to assist in the removal of devices without visible strings. Because of these risks, a woman should be offered the option

of pregnancy termination. With continuing pregnancy, it is reasonable to not attempt removal. Women pregnant with a retained device who demonstrate any evidence of uterine infection are treated with intensive antibiotic therapy and prompt uterine evacuation. In women who give birth with a device in place, appropriate steps should be taken at delivery to identify it and ensure its removal.

Ectopic Pregnancy

Although most intrauterine pregnancies are prevented, the device provides less protection against extrauterine implantation (Furlong, 2002). This is discussed in Chapter 7, Risk Factors.

CONTRAINDICATIONS

Those of the manufacturers are listed in Table 5-9. Because the progestin released by the Mirena device may inhibit tubal mobility, a previous ectopic pregnancyâ€”or predisposing risk factorsâ€”are considered contraindications.

Table 5-9 Contraindications to Use of an Intrauterine Device

General

1. Pregnancy or suspicion of pregnancy
2. Abnormalities of the uterus resulting in distortion of the uterine cavity
3. Acute pelvic inflammatory disease or a history of pelvic inflammatory disease unless there has been a subsequent uterine pregnancy
4. Postpartum endometritis or infected abortion in the past 3 months
5. Known or suspected uterine or cervical neoplasia, or unresolved abnormal cytological smear
6. Genital bleeding of unknown etiology
7. Untreated acute cervicitis or vaginitis, including bacterial vaginosis, until infection is controlled
8. Woman or her partner has multiple sexual partners
9. Conditions associated with increased susceptibility to infections with microorganisms. These include, but are not limited to, leukemia, acquired immune deficiency syndrome, and intravenous drug abuse
10. History of ectopic pregnancy or condition that would predispose to ectopic pregnancy
11. Genital actinomycosis
12. A previously inserted intrauterine device that has not been removed

ParaGard T 380A, because of its copper content, should not be inserted when one or more of the following conditions exist:

1. Wilson disease
2. Copper allergy

Mirena insertion is contraindicated when one or more of the following conditions exist:

1. Hypersensitivity to any component of this product
2. Known or suspected carcinoma of the breast
3. Acute liver disease or tumor

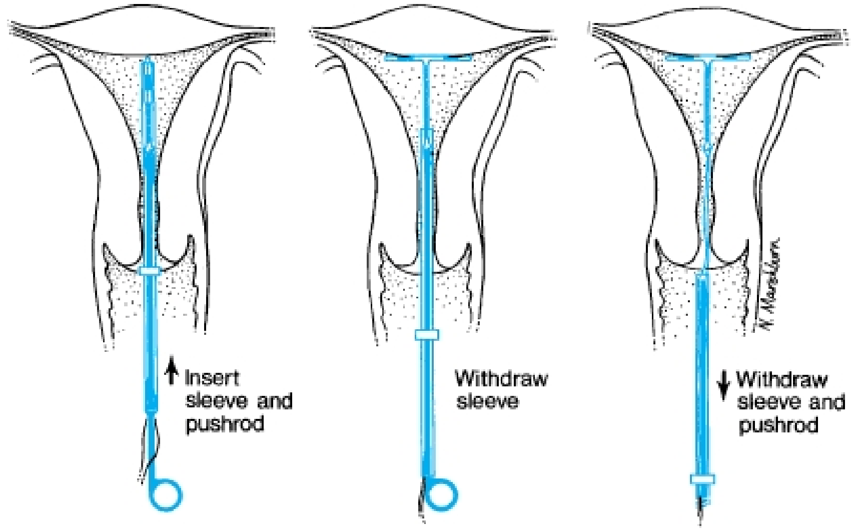
Modified from Physicians Desk Reference, 2006, with permission.

PROCEDURES FOR INSERTION

The FDA requires that before an intrauterine device is inserted, the woman must be given a brochure detailing the side effects and apparent risks from its use. Most devices have a special inserter, usually a sterile graduated plastic tube or sleeve into which the device is drawn just before insertion (Fig. 5-6). Timing of insertion influences the ease of placement as well as the pregnancy and

expulsion rates. Insertion near the end of normal menstruation, when the cervix is usually softer and the canal somewhat more dilated, may aid insertion and at the same time exclude early pregnancy. Insertion, however, need not be limited to this time. For a woman who is sure she is not pregnant and does not want to be pregnant, insertion may be carried out at anytime.

FIGURE 5-6



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Insertion of ParaGard T 380A using the withdrawal technique.

Insertion immediately postpartum is done in some countries. Grimes and colleagues (2001) surveyed the Cochrane Database and concluded that it is safe to do so, however, the expulsion rate and possibly the pregnancy rates are higher than later insertion. The recommendation has been made, therefore, to withhold insertion for at least 6 to 8 weeks to reduce expulsion rates and to minimize the risk of perforation. In our extensive experience, however, insertion at 2 weeks has not led to perforation or expulsion rates significantly higher than for later insertion. In the absence of infection, the device may be inserted immediately after early miscarriage or abortion. Women delivered at Parkland Memorial Hospital are seen at 2 to 3 weeks postpartum. Our policy is to insert IUDs at 6 weeks or sooner if involution is complete.

Technique

A satisfactory technique for insertion of the ParaGard device is as follows:

1. Determine whether there are contraindications, counsel the woman regarding various problems associated with device use, and obtain written consent.
2. Administer a nonsteroidal anti-inflammatory agent, with or without codeine, to allay cramps.
3. Perform a pelvic examination to identify the position and size of the uterus and adnexa. If abnormalities are found, they should be evaluated, as they may contraindicate the device. Mucopurulent discharge and significant vaginitis should be appropriately treated and resolved before insertion.
4. The cervical surface is cleansed with an antiseptic solution, and a tenaculum is placed on the cervical lip. The uterus is sounded, and the blue plastic flange on the outside of the inserter tube is positioned from the tube tip to reflect this depth.
5. **The device should not be loaded into its inserter tube more than 5 minutes before insertion.** The malleable arms tend to retain the "memory" of the inserter.
6. The inserter tube, with the IUD loaded, is passed into the endometrial cavity. When the blue flange abuts the cervix, insertion stops.

7. To release the arms of the ParaGard, hold the solid white rod within the tube steady and withdraw the insertion tube no more than 1 cm. This releases the arms high in the uterine fundus.
8. Gently and carefully move the insertion tube upward toward the top of the uterus until slight resistance is felt. This will ensure placement of the T at the highest possible position within the uterus.
9. Hold the insertion tube steady and withdraw the solid white rod.
10. Gently and slowly withdraw the tube from the cervical canal. Only the threads should be visible protruding from the cervix. Trim the threads so that 3 to 4 cm protrude into the vagina. Note the length of the threads in the chart.

If you suspect that the device is not in the correct position, check placement, using sonography if necessary. If it is not positioned completely within the uterus, remove it and replace it with a new device. Do not reinsert an expelled or partially expelled ParaGard device.

11. Cut the marker tail 2 cm from the external os, remove the tenaculum, and observe for bleeding from the tenaculum puncture sites. If there is no bleeding, remove the speculum.
12. Advise the woman to promptly report any apparent adverse effects.

The Mirena device requires some modifications to this technique . These are detailed in its package insert. Specifically, the arms of the device are released in the uterus *prior* to advancing it 1.5 to 2 cm to the fundus. This is accomplished by setting the flange to the sounded uterine depth, and using it to gauge, based on its 1.5- to 2-cm distance from the external os, when to release the arms. A detailed description follows:

1. Pick up the inserter containing the Mirena and carefully release the threads from behind the slider so that they hang freely.
2. Ensure that the slider is in the furthermost position away from youâ€”positioned at the top of the handle nearest the device.
3. While looking at the insertion tube, align the arms of the system horizontally.
4. Pull on both threads to draw the Mirena system into the insertion tube. Note that the knobs at the end of the arms now cover the open end of the inserter.
5. Fix the threads tightly in the cleft at the end of the handle.
6. Set the flange to the depth measured by the sound.
7. Mirena is now ready to be inserted.
8. Hold the slider firmly in the furthermost positionâ€”at the top of the handle. Grasp the cervix with the tenaculum and apply gentle traction to align the cervical canal with the uterine cavity. Gently insert the inserter tube into the cervical canal and advance the insertion tube into the uterus until the flange is situated at a distance of about 1.5 to 2 cm from the external cervical os to give sufficient space for the arms to open. **Do not force the inserter.**
9. While holding the inserter steady, release the arms of the device by pulling the slider back until the top of the slider reaches the mark, the raised horizontal line on the handle.
10. Push the inserter gently into the uterine cavity until its flange touches the cervix. The device should now be in the fundal position.
11. Holding the inserter firmly in position, release the device by pulling the slider down all the way. The threads will be released automatically.
12. Remove the inserter from the uterus. Cut the threads to leave about 2 to 3 cm visible outside the cervix.
13. If you suspect that the system is not in the correct position, check placement, using sonography if necessary. Remove the device if it is not positioned completely within the uterus. Do not reinsert a removed system.

EXPULSION

Loss of the device from the uterus is most common during the first month. The woman should be instructed to palpate the strings protruding from the cervical os by either sitting on the edge of a chair or squatting down and then advancing a finger into the vagina until the cervix is reached. The woman should be examined again in about a month, usually after menses, for appropriate

placement by identifying the tail protruding from the cervix. Barrier contraception may be desirable during this interval, especially if a device has been expelled previously.

LOST DEVICE

When the tail cannot be visualized, the device may have been expelled, or it may have perforated the uterus. In either event, pregnancy is possible. Conversely, the tail simply may be in the uterine cavity along with a normally positioned device. Often, gentle probing of the uterine cavity with a Randall stone clamp or a rod with a terminal hook will retrieve the string. **Never assume that the device has been expelled unless it was seen** .

When the tail is not visible and the device is not felt by gentle probing of the uterine cavity, sonography can be used to image the uterine cavity. If these findings are negative or inconclusive for device visualization, then a plain radiograph of the abdomen and pelvis may be obtained with a uterine sound inserted into the endometrial cavity for orientation. Instillation of radiocontrast for hysterography may also be done. Hysteroscopy is yet another alternative. Obviously none of these invasive maneuvers should be performed if a woman is pregnant and does not desire termination.

An open device of inert material, such as the Lippes Loop, located outside the uterus may or may not do harm. Large and small bowel perforations as well as bowel fistulas have been reported remote from insertion. An extrauterine copper-bearing device induces an intense local inflammatory reaction and adhesions. Chemically inert devices usually are removed easily from the peritoneal cavity by laparoscopy or colpotomy. Copper-bearing devices are more firmly adhered and laparotomy may be necessary.

A device may penetrate the uterine wall to varying degrees (Fig. 41-35.5). Part of the device may extend into the peritoneal cavity while the remainder is firmly fixed in the myometrium. Devices also can penetrate into the cervix and protrude into the vagina.

Replacement

The ParaGard device is approved for 10 years of continuous use and the Mirena device for 5 years.

Barrier Methods

For many years, condoms, vaginal spermicidal agents, and vaginal diaphragms have been used for contraception with variable success as shown in Table 5-2.

MALE CONDOM

Most condoms are made from latex rubber. Less commonly, polyurethane or the cecum of lambs is used. Condoms provide effective contraception, and their failure rate with strongly motivated couples has been as low as 3 or 4 per 100 couple-years of exposure (Vessey, 1982). Generally, and especially in the first year of use, the failure rate is much higher (see Table 5-2).

When used properly, condoms provide considerable but not absolute protection against a broad range of sexually transmitted diseases, including chlamydial, herpesvirus, and human immunodeficiency virus infection, as well as gonorrhea, syphilis, and trichomoniasis. They also may prevent and ameliorate premalignant cervical changes, probably by blocking transmission of human papillomavirus (Winer, 2006).

The contraceptive effectiveness of the condom is enhanced appreciably with a reservoir tip. Agents used for lubrication should be water based because oil-based products destroy latex condoms and diaphragms (Waldron, 1989). Speroff and Darney (2001) emphasize the following key steps to ensure maximal condom effectiveness:

1. It must be used with every coital act.
2. It should be placed before contact of the penis with the vagina.
3. Withdrawal must occur with the penis still erect.
4. The base of the condom must be held during withdrawal.
5. Either an intravaginal spermicide or a condom lubricated with spermicide should be employed.

Latex Sensitivity

Some individuals are extremely sensitive to latex. Condoms made from lamb intestines, also known as *natural skin* or *lambskin*

condoms, are effective, but they do not provide protection against infection. Because of this, a nonallergenic condom was developed using synthetic thermoplastic elastomer such as polyurethane used in surgical gloves (Mason, 1992). Polyurethane condoms are effective against sexually transmitted diseases, but have a significantly higher breakage and slippage rate than latex condoms (Frezieres, 1998; Waldron, 1991). In a randomized trial of 901 couples, Steiner and colleagues (2003) documented breakage and slippage at a rate of 8.4 percent with polyurethane condoms versus 3.2 percent with latex. Respective 6-month typical pregnancy probabilities were 9.0 versus 5.4 percent, respectively.

FEMALE CONDOM (VAGINAL POUCH)

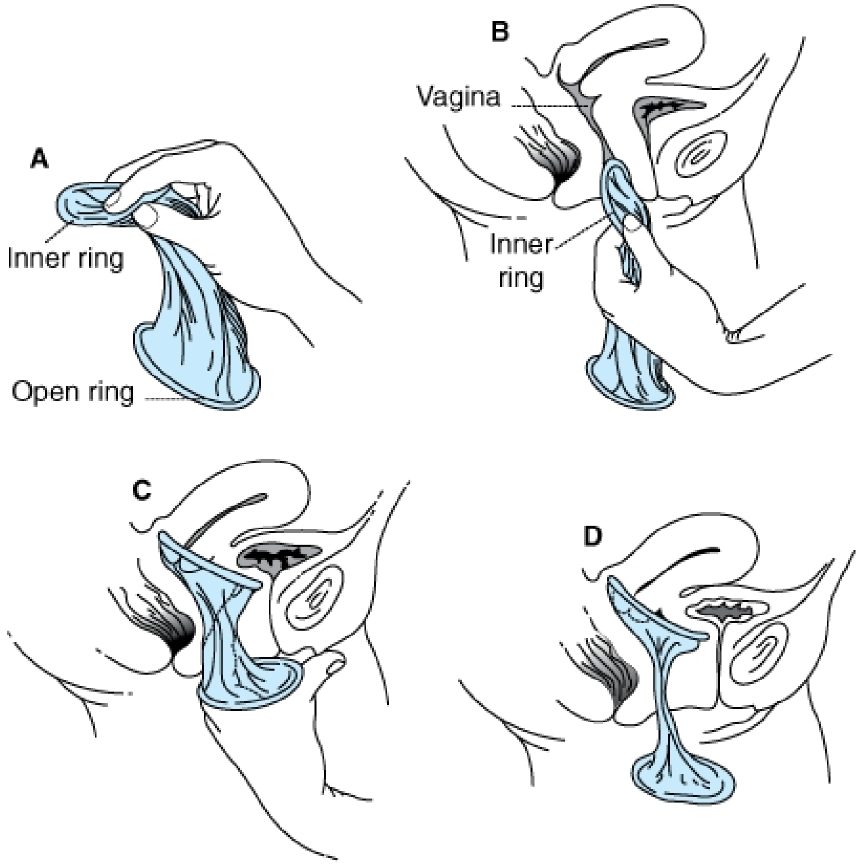
These devices prevent pregnancy and sexually transmitted diseases. They are manufactured in many countries under different names. One brand available in the United States is the *FC Female Condom* (Mayer Laboratories, Oakland, CA), which is a polyurethane sheath with a flexible polyurethane ring at each end (Fig. 5-7). The open ring remains outside the vagina, and the closed internal ring is fitted under the symphysis like a diaphragm (Fig. 5-8). In vitro tests have shown the condom to be impermeable to human immunodeficiency virus, cytomegalovirus, and hepatitis B virus. It has a 0.6 percent breakage rate. The slippage and displacement rate is about 3 percent, compared with up to 8 percent for polyurethane male condoms. It has an acceptability rate of about 60 percent for women and 80 percent for men. The pregnancy rate is higher than with the male condom (see Table 5-2).

FIGURE 5-7

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Female condom. *(Courtesy of Cervical Barrier Advancement Society.)*

FIGURE 5-8



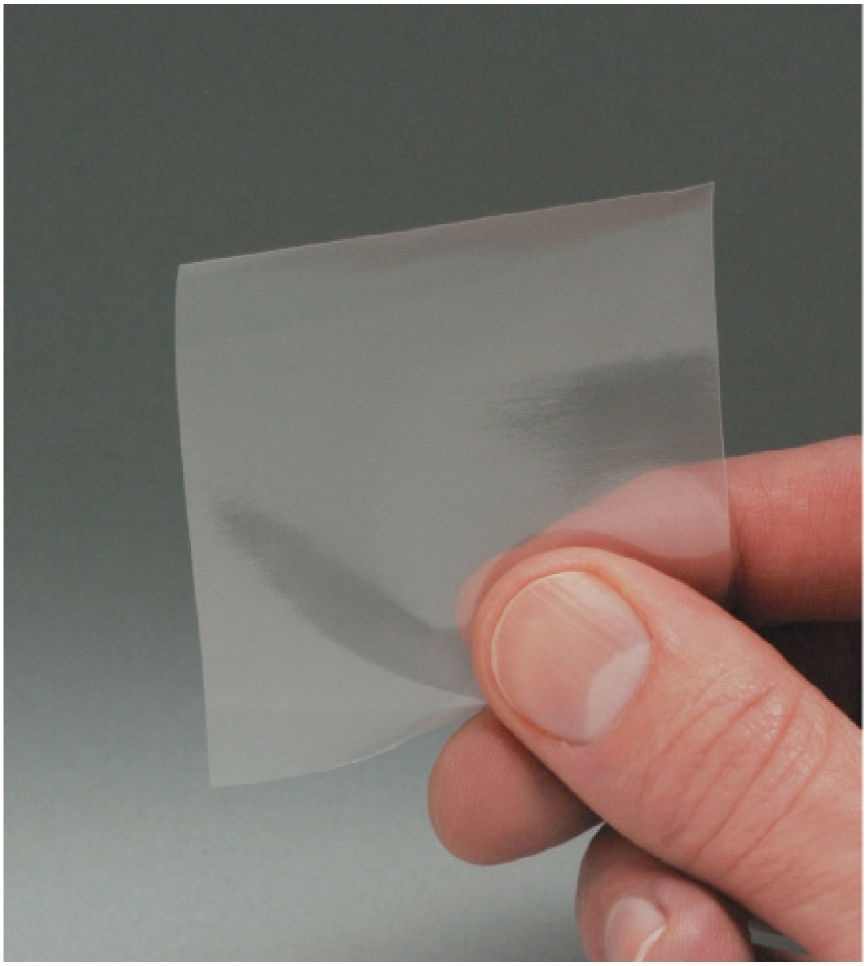
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

FC Female Condom insertion and positioning. **A.** Inner ring is squeezed for insertion. **B.** and **C.** The sheath is inserted similarly to a diaphragm and the inner ring is pushed up with the index finger as far as it can go. **D.** The vaginal pouch in place. *(Courtesy of Wisconsin Pharmacal Company, Jackson, WI.)*

SPERMICIDES AND MICROBICIDES

These contraceptives are marketed variously as creams, jellies, suppositories, film, and foam in aerosol containers (Fig. 5-9). They are used widely in this country, especially by women who find other methods unacceptable. They are useful especially for women who need temporary protection, for example during the first week after starting oral contraceptives or while nursing. Most agents can be purchased without a prescription.

FIGURE 5-9



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Vaginal contraceptive film.

Spermicides work by providing a physical barrier to sperm penetration as well as a chemical spermicidal action. The active ingredient is nonoxynol-9 or octoxynol-9. **Spermicides must be deposited high in the vagina in contact with the cervix shortly before intercourse** . Their duration of maximal effectiveness is usually no more than 1 hour. Thereafter, they must be reinserted before repeat intercourse. Douching should be avoided for at least 6 hours after intercourse.

High pregnancy rates are primarily attributable to inconsistent use rather than to method failure. Even if inserted regularly and correctly, however, foam preparations probably result in 5 to 12 pregnancies per 100 woman-years of use (Trussell, 1990). Spermicides are not teratogenic (Briggs, 2002).

Spermicides available in the United States that primarily contain nonoxynol-9 do not provide protection against sexually transmitted infections. In randomized trials, Roddy and colleagues (1998) compared nonoxynol-9, with and without condom use, and found no additional protective effects against gonorrhea, or chlamydial or HIV infection from this spermicide. Schreiber and associates (2006) recently showed that long-term use of nonoxynol-9 had minimal effects on vaginal flora.

In contrast, there is currently much interest in combination spermicides/microbicides because they are a female-controlled contraceptive method that can also protect against sexually transmitted diseases, including HIV. Shown in Table 5-10 are a number

that are under investigation. Those in the surfactant class destroy the sperm membrane as well as any viral or bacterial pathogens by disrupting their outer envelopes or membranes. Second-generation microbicides fortify natural defenses by maintaining an acidic pH or maintaining presence of antibodies and enhancing antimicrobial peptides. They also serve to maintain a hostile vaginal environment. Third-generation microbicides work as topical antiretroviral agents. Palliser and colleagues (2006) described the use of RNA interference (RNAi) to prevent herpes simplex virus 2 vaginal mucosal infections in mice. This raises possibilities of their use in microbicides (Johnson, 2006).

Table 5-10 Status of Some Current Clinical Trials of Microbicide/Spermicide Compounds

Phase	Candidate Microbicide	Organization or Developer
III	PRO 2000 (naphthalene sulfonate)	Microbicide Development Programme/Indevus
	Carraguard (carageenan)	Population Council
	Cellulose sulfate gel	GMP
	Savvy/C-31G	Family Health International/USAID/Biosyn
II/IIb	BufferGel	HIV Prevention Trials Network/Reprotect
	PRO 2000	HIV Prevention Trials Network/Indevus
II	Human monoclonal antibodies(C2FS, C2G12, C4E10)	Polymun Scientific
	Protected lactobacilli in combination with BZK	Biofem
	Tenofovir/PMPA gel	Gilead Sciences
I/II	Invisible condom	Laval University
	Praneem polyherbal	Indian Council of Medical Research
I	Acidform/Amphora	Global Microbicide Report
	Cellulose acetate phthalate	New York Blood Center/Lindsley F. Kimball Research Center
	Lactin Vaginal Capsule	Osel
	Polystyrene sulfate	India National Institute of Pharmaceutical Education and Research
	UC-781	Biosyn
	VivaGel/SPL7013	Starpharma
	TMC 120	International Partnership for Microbicides

From Weber, 2005, with permission.

DIAPHRAGM PLUS SPERMICIDE

The diaphragm consists of a circular rubber dome of various diameters supported by a circumferential metal spring (Fig. 5-10). It can be very effective when used in combination with spermicidal jelly or cream. The spermicide is applied to the cervical surface centrally in the cup and along the rim. The device is then placed in the vagina so that the cervix, vaginal fornices, and anterior vaginal wall are partitioned effectively from the remainder of the vagina and the penis. At the same time, the centrally placed

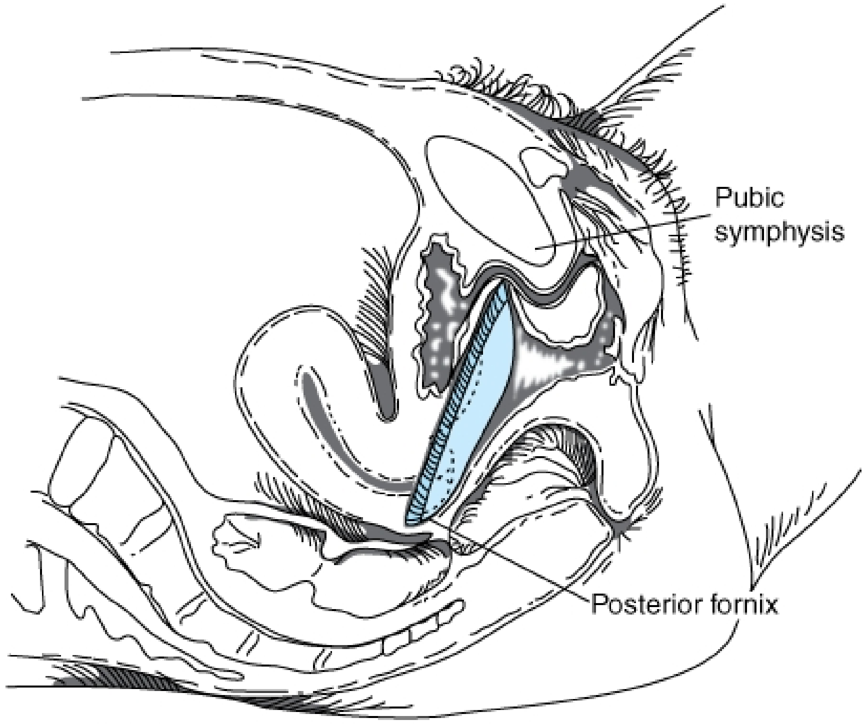
spermicidal agent is held against the cervix by the diaphragm. When appropriately positioned, the rim is lodged deep in the posterior vaginal fornix, and the opposite rim lies in close proximity to the inner surface of the symphysis immediately below the urethra (Fig. 5-11). If the diaphragm is too small, it will not remain in place. If too large, it will be uncomfortable when forced into position. Because the variables of size and spring flexibility must be specified, the diaphragm is available only by prescription (Allen, 2004).

FIGURE 5-10

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Group of three diaphragms. *(Courtesy of Cervical Barrier Advancement Society.)*

FIGURE 5-11



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

A diaphragm in place creates a physical barrier between the vagina and cervix, and importantly, provides for intimate contact between the contraceptive jelly or cream and the cervix.

The diaphragm and spermicidal agent can be inserted hours before intercourse, but if more than 2 hours elapse, additional spermicide should be placed in the upper vagina for maximum protection and be reapplied before each coital episode. The diaphragm should not be removed for at least 6 hours after intercourse. Because *toxic shock syndrome* has been described following its use, the diaphragm should not be left in place for longer than 24 hours (see Chap. 3, Toxic Shock Syndrome).

The diaphragm requires a high level of motivation for proper use. Vessey and colleagues (1982) reported a pregnancy rate of only 1.9 to 2.4 per 100 woman-years for motivated users. In a small study, Bounds and associates (1995) reported a much higher failure rate of 12.3 per 100 woman-years. The unintended pregnancy rate is lower in women older than 35 years than in those younger than 30.

Diaphragm use results in a lower incidence of sexually transmitted diseases compared with condom use (Rosenberg, 1992). Conversely, there is a slight increase in the rate of urinary infections with this method (Hatcher, 2004). A diaphragm may not be an effective choice for women with significant pelvic organ prolapse. Prolapse may result in unstable diaphragm positioning and expulsion.

CONTRACEPTIVE SPONGE

Off the market for 8 years in the United States, the *Today* contraceptive sponge (Allendale Pharmaceuticals, Allendale, NJ) is again available. It is sold over the counter, and consists of a nonoxynol-9 impregnated polyurethane disc which can be inserted up to 24 hours prior to intercourse (Fig. 5-12). After moistening, it is placed directly against the cervix. While in place, it provides contraception regardless of the frequency of coitus. It should remain in place for 6 hours after intercourse. Although perhaps more convenient, it is less effective than the diaphragm and condom (see Table 5-2).

FIGURE 5-12

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Today brand vaginal sponge.

CERVICAL CAP

The *Prentif* cavity-rim cervical cap is a flexible, cup-like device, made of natural rubber that is fitted around the base of the cervix (Fig. 5-13A). It can be self-inserted and allowed to remain in place for up to 48 hours. It should be used with a spermicide applied once at insertion. If properly fitted and used correctly, the cap is comparable in effectiveness to the diaphragm (Bernstein, 1982; Richwald, 1989). The cap is relatively costly, and in practice, incorrect fitting or improper placement make it less effective overall than the diaphragm and spermicide (see Table 5-2). Due to lack of interest and a small market share, the Prentif cap is no longer manufactured in the United States but it is available from European manufacturers.

FIGURE 5-13

A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

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A. Prentif cavity-rim cervical cap. **B.** Lea's shield. *(Courtesy Cervical Barrier Advancement Society.)*

LEA'S SHIELD

This is a reusable, washable, barrier made of silicone which is placed against the cervix (Fig. 5-13B). The device comes in one size which simplifies the fitting process. *Lea's Shield* (Yama, Inc., Union, NJ) protects against pregnancy and sexually transmitted infections. It may be inserted any time prior to intercourse and must be left in place for at least 8 hours after. When used with spermicide, and adjusted for age, the reported 6-month life table pregnancy rate was 5.6 per 100 users (Mauck, 1996).

FERTILITY-AWARENESS BASED METHODS

This is defined by the World Health Organization as a method that involves identification of the fertile days of the menstrual cycle. The couple may then avoid intercourse or use a barrier method during those days. The comparative efficacy of fertility-awareness based methods remains unknown (Grimes, 2004). Clearly, proper instruction is critical and complex charting is involved. These charts, as well as detailed advice, are available from the National Fertility Awareness and Natural Family Planning Service for the United Kingdom (http://www.fertilityuk.org) and The Natural Family Site, BYG Publishing (http://www.bygpub.com/natural).

Standard Days Method

This method, developed by the Institute for Reproductive Health at Georgetown University, is based on self-reported regular monthly cycles of 26 to 32 days during which users avoid unprotected intercourse during cycle days 8 through 19. Women who use the *standard days method* can use *CycleBeads* (Cycle Technologies, Washington, DC) to keep track of their days (Fig. 5-14) (Arevalo, 2002).

FIGURE 5-14

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

CycleBeads.

Periodic or Rhythmic Abstinence

Because the human ovum is probably susceptible to successful fertilization for only about 12 to 24 hours after ovulation, and because sperm can live up to 6 days in the reproductive tract, periodic abstinence has intuitive appeal as a means of birth control. Pregnancy rates, however, with various methods of periodic abstinenceâ€”rhythm, natural family planning, or fertility-awareness based methodsâ€”have been estimated from 5 to 40 per 100 woman-years. Put another way, the unwanted pregnancy rate during the first year of use is approximately 20 percent (see Table 5-2).

CALENDAR RHYTHM METHOD

Ovulation most often occurs about 14 days before the onset of the next menstrual period, and unfortunately, not necessarily 14 days *after* the onset of the last menstrual period. Therefore, the *calendar rhythm method* is not reliable. The International Planned Parenthood Federation (1982) concluded that "couples electing to use periodic abstinence should, however, be clearly informed that the method is not considered an effective method of family planning".

TEMPERATURE RHYTHM METHOD

The temperature rhythm method relies on *slight* changes (a sustained 0.4Â°F increase) in the morning basal body temperature that usually occurs just before ovulation (see Fig. 19-4). This method is much more likely to be successful if, during each menstrual cycle, intercourse is avoided until well after the ovulatory temperature rise. For this method to be most effective, the woman must abstain from intercourse from the first day of menses through the third day after the increase in temperature. For obvious reasons, this is not a popular method, but with excellent compliance, the unwanted pregnancy rate is only about 2 percent the first year.

CERVICAL MUCUS RHYTHM METHOD

The so-called *Billings method* depends on awareness of vaginal "dryness" and "wetness". These are the consequence of changes in the amount and quality of cervical mucus at different times in the menstrual cycle (see Chap. 19, Cervical Factors). Abstinence is required from the beginning of menses until 4 days after slippery mucus is identified. Although this method is also not popular, when it is used accurately, the first-year failure rate is only about 3 percent.

SYMPTOTHERMAL METHOD

This system combines the use of changes in cervical mucusâ€" onset of the fertile period; changes in basal body temperatureâ€"end of the fertile period; and cycle day calculations to estimate the time of ovulation. Although more complex to learn and apply, the system does not appreciably improve reliability. The use of home kits to detect luteal hormone increases in the urine on the day prior to ovulation may improve the accuracy of periodic abstinence methods (Hatcher, 2004).

SPECIAL CONSIDERATIONS FOR CONTRACEPTION

There are a number of unique circumstances that present special challenges for assuming contraceptive efficacy while minimizing undesirable effects.

Adolescents

Menarche has decreased from about age 17 in the mid-1800s to near 12 years by 2001. Reproductive function is established earlier than psychological understanding of the consequences of sexual activity. Early sexual development far too often results in intermittent spontaneous sexual encounters and a naÃ¯ve perception of the risks of pregnancy and sexually transmitted diseases (see Chap. 14, Adolescent Perceptions of Sexual Activity) (Cromer, 1996; Sulak, 1993).

Contraception is most often sought more than a year after sexual activity has begun (Mosher, 1991). Concerns about confidentiality and lack of money deter adolescents from seeking and obtaining contraception (American College of Obstetricians and Gynecologists, 2003b). Both barriers are surmountable, and in most cases, should not impede access to contraception. Indeed, in most states, minors have explicit legal authority to consent to contraceptive services. In many areas, publicly funded clinics provide free contraception to adolescents (Alan Guttmacher Institute, 2002).

COMBINATION ORAL CONTRACEPTIVES

As a method, these agents are an excellent choice for this age group because they provide effective contraception, increased bone density, and can be used to improve acne and regulate irregular menses. The obvious disadvantage is the daily requirement of pill taking.

LONG-ACTING METHODS

Injectable depot medroxyprogesterone is an effective contraceptive that also may be considered a "use and forget" method for 3 months. The disadvantages include the need for injection every 3 months, menstrual irregularities, and loss of bone mass (Sulak,

1999).

BARRIER METHODS

Despite their obvious advantage of providing some protection against sexually transmitted diseases, barrier methods are not good choices for adolescents because they require preplanning and motivation for proper use. Such methods, especially vaginal spermicides and male condoms, should be considered primarily as backup contraceptives and protective methods for sexually transmitted diseases. Intrauterine devices may be considered for adolescents who are at low risk of sexually transmitted diseases (Edelman, 1990; Prager, 2007).

Contraceptive Choices for Women Older Than 35 Years

Although fertility begins to decline at about age 35 to 40 years, there is still the risk for unwanted pregnancy and sexually transmitted diseases. Henshaw (1998) reported that half of all pregnancies in women in their 40s are unintended, and that 65 percent of these are terminated. The primary method of concern for birth control in women older than 35 is among those who smoke and who use combination hormonal contraception. This also includes women who use nicotine in any form. None of them should use COCs because the risk of myocardial infarction is increased up to 11-fold compared with similarly aged women not using oral contraceptives (Myocardial Infarction).

COMBINATION ORAL CONTRACEPTIVES

These agents are highly effective, well tolerated, provide many health benefits, and are associated with minimal risk (Beck, 1995; Speroff, 1995). According to the American College of Obstetricians and Gynecologists (2000b), healthy, nonsmoking women may use combination oral contraceptives containing less than 50 μg of estrogen until the menopause.

INJECTABLE DEPOT MEDROXYPROGESTERONE

This is a highly effective hormonal contraceptive that can also be used by some women who cannot, for medical reasons, take COCs (Speroff, 1995). Because of the association with bone loss, this method should be used with caution for longer than 2 years in perimenopausal women.

INTRAUTERINE DEVICE

This method is a logical choice for an older woman who has completed her family and is in a monogamous relationship.

BARRIER TECHNIQUES AND SPERMICIDAL AGENTS

These methods can be used either as primary or adjunct contraception. Their effectiveness improves with advancing age in those older than 40 years, likely because of diminished fertility.

Women with Medical Conditions

Pregnancies in women with medical complications often result in dangers that far exceed those seen with most forms of contraception (American College of Obstetricians and Gynecologists, 2000b). The choice of the most effective and safest method of contraception is dependent on the disease, and how it is modified by pregnancy.

Lactation

Breast feeding is important to infant health and to child spacing. For mothers who are nursing, ovulation during the first 10 weeks after delivery is unlikely (PÃ©rez, 1981). Nursing, however, is not a reliable method of family planning for women whose infants are on a daytime-only feeding schedule. **Waiting for first menses involves a risk of pregnancy because ovulation usually antedates menstruation** . Certainly, after the first menses, contraception is essential unless a woman desires pregnancy.

According to the American College of Obstetricians and Gynecologists (2000a), progestin-only oral contraceptives are the preferred choice in most cases (Benefits). Estrogen-progestin contraceptives have been assumed to possibly reduce both the rate and the duration of milk production. However, in a systematic review of randomized trials of contraceptives during lactation, Truitt and colleagues (2003) concluded that there is insufficient evidence to establish any effect of hormonal contraception on milk quality and quantity. The benefits from pregnancy prevention by use of oral contraceptives outweigh the risks.

Intrauterine devices have also been recommended for lactating, sexually active women. There is a very small increased rate of uterine perforation in lactating women who wear an IUD, perhaps from vigorous myometrial contractions caused by oxytocin release in response to suckling (Heartwell, 1983).

STERILIZATION

In the United States in 2002, surgical sterilization was the most commonly reported form of contraception in women aged 35 to 44 years (Bensyl, 2005). The number of sterilization procedures cannot be tracked accurately because most interval tubal sterilizations and vasectomies are performed in ambulatory centers. Westhoff and Davis (2000), citing data from the National Survey of Family Growth, estimate that about 700,000 tubal sterilizations are performed annually. A number of important multicenter studies of voluntary sterilization have been performed by investigators of the United States Collaborative Review of Sterilization (CREST) and the Centers for Disease Control and Prevention. Many of their observations are subsequently described.

Female Sterilization

This is the contraceptive method of choice for 28 percent of couples in the United States (American College of Obstetricians and Gynecologists, 2003a). It is usually accomplished by occlusion or division of the fallopian tubes to prevent an unfertilized ovum from passing through the fallopian tubes where it can be fertilized by sperm. This can be performed at any time, but at least half of tubal sterilization procedures are done at the time of cesarean or vaginal delivery (MacKay, 2001). Nonpuerperal tubal sterilization is usually accomplished via laparoscope in an outpatient surgical center. Microlaparoscopy is a growing technique that affords the opportunity to perform female sterilization in an office setting, using local analgesia and smaller incisions.

INDICATIONS FOR FEMALE STERILIZATION

The indication for this elective procedure is a request for sterilization with clear understanding that this is a permanent and irreversible procedure. A woman should be counseled regarding alternative choices for contraception (American College of Obstetricians and Gynecologists, 2007).

CONTRAINDICATIONS

Although there are few true contraindications to tubal sterilization other than those pertaining to surgical risks, there are many cautions to be considered before performing the surgery.

CAUTIONS

There will invariably be a number of women who express *regrets about sterilization.* From the CREST study, Jamieson and coworkers (2002) reported that by 5 years, 7 percent of women undergoing tubal ligation had regrets. This is not limited to their own sterilization because 6.1 percent of women whose husbands had undergone vasectomy had similar regrets. The cumulative probability of expressing regret during a subsequent interview within 14 years of tubal sterilization was 20 percent for women aged 30 or younger at sterilization, compared with only 6 percent for those over 30 years (Hillis, 1999). Importantly, 93 percent of women who undergo sterilization have no regrets.

NONPUERPERAL (INTERVAL) TUBAL STERILIZATION

These techniques, including any modifications, basically consist of:

1. Ligation and resection at minilaparotomy, as described earlier for puerperal sterilization (see Section 41-24, Interval Partial Salpingectomy).
2. The application of a variety of permanent rings or clips to the fallopian tubes, usually by laparoscopy (see Section 41-29, Laparoscopic Sterilization).
3. Electrocoagulation of a segment of the oviducts, also usually through a laparoscope (see Section 41-29, Laparoscopic Sterilization).

Surgical Approaches

There are a number of approaches and techniques to perform nonpuerperal tubal sterilization. In developed countries, including the United States, laparoscopic tubal ligation is the leading method used for female sterilization (American College of Obstetricians and

Gynecologists, 2003a). The procedure is frequently done in an ambulatory surgical setting under general anesthesia. The woman can almost always be discharged several hours later. The actual disruption of tubal continuity is accomplished using loops, clips, or electrocoagulation with and without transection of the tube. Because electrocoagulation destroys a large segment of tube, surgical reversal is usually difficult and often not possible.

Minilaparotomy using a 3-cm suprapubic incision is popular, especially in resource-poor countries (Kulier, 2002). The peritoneal cavity can also be entered by colpotomy or culdotomy through the posterior vaginal fornix, although this approach is not commonly used today.

Major morbidity is rare with either laparoscopy or minilaparotomy. In the study by Kulier and associates (2002), minor morbidity was twice as common in the minilaparotomy group.

Methods of Tubal Interruption

A number of techniques or devices can be used to accomplish tubal sterilization via laparoscopy. Details of these have been provided by a number of reviewers. In a Cochrane Review, Nardin and colleagues (2003) concluded that all techniques of interval sterilization are effective in preventing pregnancy. There is not enough evidence to determine which technique is most effective, nor which technique has the most complications because these are uncommon. That said, pregnancy is less likely with an experienced operator, thus the method chosen is usually based on expertise and preferences of the surgeon.

Electrocoagulation is used for destruction of a segment of tube and can be accomplished with either unipolar or bipolar electric current. Although unipolar coagulation has the lowest long-term failure rate, it also has the highest serious complication rate. For this reason, bipolar coagulation rather than unipolar, is favored by most (American College of Obstetricians and Gynecologists, 2003a). When three or more sites are coagulated, the 5-year cumulative probability of pregnancy is about 3 per 1,000 procedures compared with 12 per 1,000 when fewer than three sites are coagulated (Peterson, 1999).

Mechanical methods of tubal occlusion can be accomplished with a silicone rubber band such as the *Falope Ring* and the *Tubal Ring;* the spring-loaded *Hulka-Clemens Clip,* also known as the *Wolf Clip;* or the silicone-lined titanium *Filshie Clip.* Sokal and co-workers (2000) compared the Tubal Ring and Filshie Clip in a randomized trial of 2,746 women and reported similar rates of safety as well as a 1-year pregnancy rate of 1.7 per 1,000 women. All of these methods have a favorable long-term success rate. When done via laparoscopy, these procedures are technically more difficult and they have significantly higher failure rates before experience is gained (Peterson, 2001).

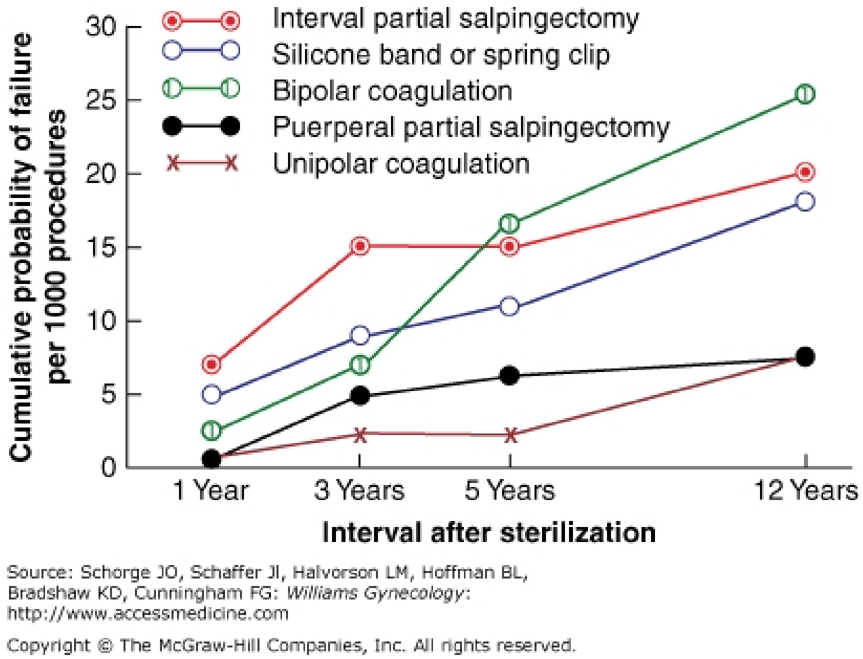
Failure Rates

The reasons for interval tubal failures are not always apparent, but include:

1. Surgical errors, which likely account for 30 to 50 percent of cases.
2. An occlusion-method failure may be due to fistula formation, especially with electrocoagulation procedures. This is less likely now that use of an ammeter is standard. Faulty clips may not be occlusive enough, or the fallopian tube may spontaneously undergo reanastomosis.
3. Equipment failure, such as a defective electric current for the electrocoagulation, may be causative.
4. In some cases, the woman was already pregnant at the time of surgeryâ€”a so-called *luteal phase pregnancy.*

From the CREST studies, 1.3 percent of 10,685 tubal sterilizations were followed by subsequent pregnancy. As shown in Fig. 5-15, some sterilization methods have lower failure rates than others. Even with the same procedure, there are variations in failure rate. For example, when a silicone band was applied solely to the distal portion of at least one fallopian tube, failure rates were higher than if a band was applied to a different portion of the tube (Peterson, 2001).

FIGURE 5-15



Data from the U.S. Collaborative Review of Sterilization (CREST) shows the cumulative probability of pregnancy per 1,000 procedures by five methods of tubal sterilization. *(Data from Peterson, 1996, with permission.)*

The lifetime increased cumulative failure rates over time are supportive that failures after 1 year are not likely due to technical errors. Soderstrom (1985) found that most sterilization failures were not preventable.

Long-Term Complications

In addition to the 15-year cumulative pregnancy rates shown in Figure 5-15, there are other long-term adverse effects as discussed below.

Ectopic Pregnancy

As many as 65 percent of pregnancies that follow a failed electrocoagulation procedure are ectopic, compared with only 10 percent following failure of a ring, clip, or tubal resection method (Hatcher, 1990; Hendrix, 1999; Peterson, 1999). Any symptoms of pregnancy in a woman after tubal sterilization must be investigated, and an ectopic pregnancy must be excluded. Diagnosis and management are discussed in detail in Chapter 7.

Postâ€"Tubal Ligation Syndrome

In 1951, Williams and colleagues described their 22-year experience with long-term evaluation of women who had undergone tubal ligation. They reported an excessive incidence of menorrhagia and intermenstrual bleeding. This later became known as the *postâ€"tubal ligation syndrome.* Subsequently, a similar incidence of menstrual dysfunction was reported in women whose husbands had undergone vasectomy (DeStefano, 1985; Shy, 1992). Since then, debate over the very existence of a unique syndrome has persisted.

Observations from the CREST study are very informative concerning these issues. Peterson and colleagues (2000) compared long-term outcomes of 9,514 women who had undergone tubal sterilization with a cohort of 573 women whose partners had undergone vasectomy. They found that both groups had similar risks for menorrhagia, intermenstrual bleeding, and dysmenorrhea. Women who had undergone sterilization had *decreased* duration and volume of menstrual flow and *less* dysmenorrhea. There was, however, an increased incidence of cycle irregularity in the sterilized women. Harlow and co-workers (2002) reported no significant change in serum levels of FSH, LH, and estradiol in these women. Timonen and co-workers (2002) reported a transient increase in follicular phase serum estradiol levels that normalized by 12 months. Currently, the cause of these findings remains an enigma.

Other Effects

It is controversial whether the incidence of *subsequent hysterectomy* is increased in women who have undergone tubal sterilization (Mall, 2002; Pati, 2000). In a CREST surveillance study, Hillis and associates (1997) reported that 17 percent of women undergoing tubal sterilization had also undergone hysterectomy by 14 years. Although they did not compare this incidence with a cohort control, the indications were similar to those for nonsterilized women undergoing hysterectomy.

Westhoff and Davis (2000) concluded that tubal sterilization likely protects against subsequent *ovarian cancer.* They found no differences in the incidence of subsequent *breast cancer.* According to Holt and colleagues (2003), the incidence of *functional ovarian cysts* is increased almost twofold following tubal sterilization. Levgur and Duvivier (2000) reported that women who had undergone tubal sterilization were highly unlikely to have subsequent *salpingitis* .

Less objective but important psychological sequelae of sterilization have also been evaluated. From the CREST Study, Costello and colleagues (2002) found that tubal ligation did not change *sexual interest or pleasure* in 80 percent of women. The majority of the remaining 20 percent who did report a change, were 10 to 15 times more likely to have *positive effects* .

TUBAL STERILIZATION REVERSAL

No woman should undergo tubal sterilization believing that subsequent fertility is guaranteed by either surgery or assisted reproductive techniques. These latter procedures are technically difficult, expensive, and not always successful. Success rates vary greatly depending on the woman's age, the amount of tube remaining, and the technology used. Van Voorhis (2000) reviewed a number of reports and found that pregnancy rates varied from 45 to 90 percent with surgical reversals. For example, pregnancy rates as high as 80 percent have been reported for tubal reanastomosis (Cha, 2001). When neosalpingostomy is done for fimbriectomy reversal, however, successful pregnancies develop in only 30 percent (Tourgeman, 2001). **Almost 10 percent of women undergoing tubal sterilization reversal have an ectopic pregnancy** .

Reversal procedures can be done by laparoscopy or laparotomy, and pregnancy rates are similar with either method (Cha, 2001). In a cost-effectiveness study from Canada, Hawkins and associates (2002) found laparoscopy to have lower costs than laparotomy.

HYSTERECTOMY

For the woman who desires no more children, hysterectomy has many theoretical advantages. In the absence of uterine or other pelvic disease, however, hysterectomy solely for sterilization is difficult to justify.

TRANSCERVICAL STERILIZATION

Sterilization has been performed by using hysteroscopy to visualize the tubal ostia and obliterating them with a variety of compounds or devices.

Intratubal Chemical Methods

Use of a few older methods persists, and a number of new compounds are under investigation (Ballagh, 2003). *Silicone plugs* form after silicone liquid is injected transcervically into the tubes where it hardens. Repeat procedures are needed in 20 percent of women and continued tubal patency is common. Tubal injections with the adhesive *methylcyanoacrylate* cause inflammation, necrosis, and fibrosis. Insertion of *quinacrine pellets* has been used to achieve tubal occlusion in over 100,000 women in other countries. Because of concerns of carcinogenesis from a study of 30,000 Vietnamese women, however, the WHO recommended halting quinacrine usage (Lippes, 2002). Likewise, *erythromycin* placed tubally to incite inflammation has been investigated, but it has an unacceptably high 1-year failure rate of 36 percent (Bairagy, 2004).

Intratubal Devices

In contrast to chemical methods, mechanical devices can be inserted into the proximal fallopian tube using a hysteroscope. Several devices have been evaluated and the *Essure System* (Conceptus, Mountain View, CA) was approved by the FDA in 2002. This device is a microinsert that has a stainless steel inner coil enclosed in polyester fibers and an expandable outer coil of *nitinol* â€”a nickel and titanium alloy used in coronary artery stents (see Section 41-42, Hysteroscopic Placement of Essure Microinserts). The outer coil expands after placement, allowing the fiber to also expand, and as tissue grows within the fiber, tubal occlusion results.

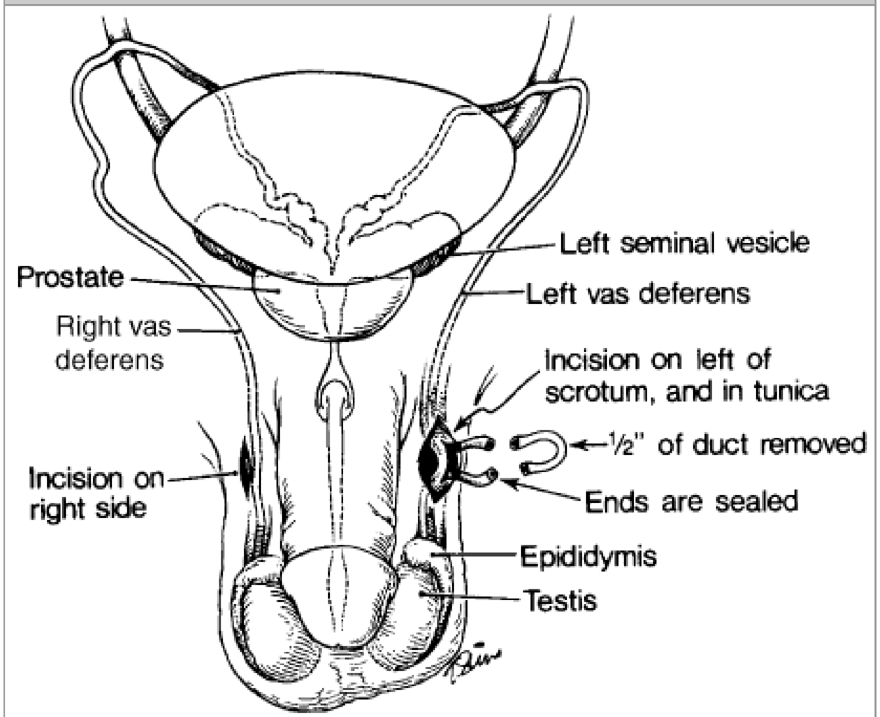
One advantage of the Essure System is that placement can be done as an office hysteroscopy procedure. One major drawback of Essure placement, however, is that a hysterosalpingography must be done at 3 months to assure tubal blockage. Some studies have evaluated the effectiveness of sonography to confirm correct placement (Kerin, 2005; Weston, 2005). Another disadvantage is that the device alone costs almost 1,000 U.S. dollars.

Preliminary results with this and other devices have been encouraging (Association of Reproductive Health Professionals, 2002). Investigators describe use of sedation or paracervical block, or both prior to hysteroscopic placement of Essure microinserts (Cooper, 2003; Mino, 2007). Cooper and associates (2003) reported proper insertion in 464 of 507 women (92 percent). In these women, there had been no pregnancies by 9,620 woman-months. In a similar study, Kerin and colleagues (2001) reported that 97 percent of women expressed very good to excellent satisfaction after 2 years.

Male Sterilization

Nearly a half million men in the United States undergo vasectomy each year (Magnani, 1999). Through a small incision in the scrotum, the lumen of the vas deferens is disrupted to block the passage of sperm from the testes (Fig. 5-16). With local analgesia, the procedure is usually performed within 20 minutes. In their review, Hendrix and colleagues (1999) found that compared with vasectomy, female tubal sterilization has a 20-fold increased complication rate, 10- to 37-fold increased failure rate, and a threefold increased cost. In Dallas in 2006, total charges for a vasectomy were $1,050 compared with almost $5,000 for an outpatient laparoscopic tubal ligation.

FIGURE 5-16



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Schematic showing anatomy and procedure for vasectomy.

A disadvantage of vasectomy is that sterility is not immediate. Complete expulsion of sperm stored in the reproductive tract beyond the interrupted vas deferens takes about 3 months or 20 ejaculations (American College of Obstetricians and Gynecologists, 1996). Although most recommend that semen should be analyzed until two consecutive sperm counts are zero, Bradshaw and colleagues (2001) reported that only one azoospermic semen analysis is sufficient. Before azoospermia is documented, another form of

contraception must be used.

The failure rate for vasectomy is much less than 1 percent (Schwingl, 2000). These include failures from unprotected intercourse too soon after ligation, failure to occlude the vas deferens, or recanalization. There is a phenomenon termed *transient sperm reappearance* that usually is not associated with pregnancy. Haldar and co-workers (2000) described temporary low sperm counts in 20 of 2,250 men who had been documented to have azoospermia following vasectomy. Their sperm counts were less than 10,000/mL, and in the 14 retested 1 month later, azoospermia was again confirmed. They concluded that spermatozoa present in the distal vas deferens are slowly released, or that microchannels form with sperm granulomas.

RESTORATION OF FERTILITY

Success after vasectomy reversal depends on several factors. A review of several reports suggests that odds for success are about 50 percent, with somewhat higher rates following microsurgical reanastomosis.

LONG-TERM EFFECTS

Other than regrets, long-term consequences are rare (Amundsen, 2004). After vasectomy, antibodies directed at spermatozoa can frequently be identified. Concern was raised over the possibility that the immune response might cause harmful systemic changes. Despite this, studies have not identified an increase in cardiovascular disease, circulating immune complexes, or damage to retinal blood vessels (Giovannucci, 1992; Goldacre, 1983). Subsequently, Manson and associates (1999) provided data from 1,159 physicians in the U.S. Physicians' Health Study. In a 15-year surveillance, there was no difference in the incidence of myocardial infarction or stroke in men with or without vasectomy. From their review, Schwingl and Guess (2000) also concluded that vasectomy is not followed by accelerated atherogenesis.

There is no convincing evidence of an increased incidence of testicular cancer following vasectomy (Giovannucci, 1992). Earlier studies found no evidence to associate development of *prostatic carcinoma* with vasectomy (Giovannucci, 1993a, 1993b; Hayes, 1993). This changed, however, when Lesko and colleagues (1999) compared surveillance results in 1,216 vasectomized men and 1,400 controls. They reported an almost twofold risk of prostatic cancer in men less than 55 years, but not in older men. Following this, a population-based Danish cohort study found that prostatic cancer was not increased (Lynge, 2002). These findings indicate, at worst, a weak association that may be explicable by greater scrutiny of men who underwent vasectomy (GrÃ¶nberg, 2003).

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Note: Large images and tables on this page may necessitate printing in landscape mode.

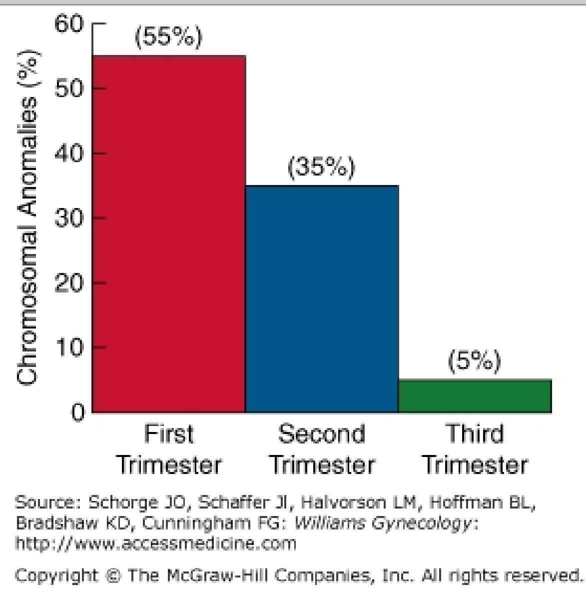
FIRST-TRIMESTER ABORTION: INTRODUCTION

Abortion is the spontaneous or induced termination of pregnancy before fetal viability. Because popular use of the word *abortion* implies a deliberate pregnancy termination, some prefer the word miscarriage to refer to spontaneous fetal loss before viability. Because the widespread use of sonography and serum measurement of human chorionic gonadotropin levels allows identification of an extremely early pregnancy, a number of other names have come into common use. These include, for example, *early pregnancy loss* or *early pregnancy failure* . The National Center for Health Statistics, the Centers for Disease Control and Prevention (CDC), and the World Health Organization (WHO) define *abortion* as pregnancy termination prior to 20 weeks' gestation or a fetus born weighing less than 500 g. Despite this, definitions vary widely according to state laws.

MISCARRIAGE, SPONTANEOUS ABORTION, OR EARLY PREGNANCY FAILURE

More than 80 percent of spontaneous abortions are in the first 12 weeks of pregnancy. As shown in Fig. 6-1, at least half result from chromosomal anomalies. There also appears to be a 1.5 male:female gender ratio in early abortuses (Benirschke, 2000). After the first trimester, both the abortion rate and the incidence of associated chromosomal anomalies decrease.

FIGURE 6-1



Frequency of chromosomal anomalies in abortuses and stillbirths during each trimester. Approximate percentages for each group are shown. *(Data from Eiben, 1990, Fantel, 1980, and Warburton, 1980, with permission.)*

Hemorrhage into the decidua basalis, followed by necrosis of tissues adjacent to the bleeding, usually accompanies early miscarriage. In these cases, the ovum detaches, stimulating uterine contractions that result in its expulsion. When a gestational sac is opened, fluid is commonly found surrounding a small macerated fetus, or alternatively no fetus is visibleâ€"the so-called *blighted ovum* .

Incidence

In a meticulous investigation of 221 healthy women studied through 707 menstrual cycles, Wilcox and colleagues (1988) reported that 31 percent of pregnancies are lost after implantation. They used highly specific assays for minute concentrations of β-human chorionic gonadotropin (β-hCG) and reported that two thirds of these early loses were *clinically silent* .

A number of factors influence the spontaneous abortion rate, and it is not known if those that are clinically silent are affected. For example, clinically apparent miscarriage increases with parity as well as with maternal and paternal age (Gracia, 2005; Warburton, 1964; Wilson, 1986). The frequency doubles from 12 percent in women younger than 20 years to 26 percent in those older than 40. For the same comparison of paternal ages, the frequency increases from 12 to 20 percent. Again, it is not known if clinically silent miscarriages are similarly affected by these factors.

Although mechanisms responsible for abortion are not always apparent, during the first 3 months of pregnancy, death of the embryo or fetus nearly always precedes spontaneous expulsion. Thus, finding the cause of early abortion involves ascertaining the cause of fetal death. In later losses, the fetus usually does not die before expulsion and other explanations are sought.

Fetal Factors

Early spontaneous abortions commonly display a developmental abnormality of the zygote, embryo, early fetus, or at times the placenta. Of 1,000 spontaneous abortions analyzed by Hertig and Sheldon (1943), one-half had a degenerated or absent embryo, which are the blighted ova described previously. In 50 to 60 percent of spontaneously aborted embryos and early fetuses, abnormalities in chromosomal numbers account for most wastage (Table 6-1).

Table 6-1 Chromosomal Findings in Abortuses

	Incidence in Percent		
Chromosomal Studies	**Kajii (1980)**	**Eiben (1990)**	**Simpson (2002)**
Normal (euploid)			
46, XY and 46, XX	46	51	54
Abnormal (aneuploid)			
Autosomal trisomy	31	31	22
Monosomy X (45, X)	10	5	19
Triploidy	7	6	8
Tetraploidy	2	4	3
Structural anomaly	2	4	3
Double or triple trisomy	2	0.9	0.7

ANEUPLOID ABORTION

About 95 percent of chromosomal abnormalities are caused by maternal gametogenesis errors, 5 percent are due to paternal errors (Jacobs, 1980). Those found most commonly in abortuses are listed in Table 6-1.

Autosomal trisomy is the most frequently identified chromosomal anomaly with first-trimester miscarriages. Although most trisomies result from *isolated nondisjunction* , balanced structural chromosomal rearrangements are present in one partner in 2 to 4 percent of couples with recurrent miscarriage (American College of Obstetricians and Gynecologists, 2001). Autosomal trisomies for all except chromosome number 1 have been identified in abortuses, and those with autosomes 13, 16, 18, 21, and 22 are most common. Bianco and colleagues (2006) recently described that a previous miscarriage increased the risk of a subsequent fetal aneuploidy to 1.67 percent from a baseline risk of 1.39 percent in almost 47,000 women. Two or three previous miscarriages

increased this to 1.84 and 2.18 percent, respectively.

Monosomy X (45, X), is the single most common specific chromosomal abnormality. These cause Turner syndrome, which usually results in abortion and much less frequently in live-born females (see Chap. 16, Abnormal Karyotype). Conversely, *autosomal monosomy* is rare and incompatible with life.

Triploidy is often associated with hydropic placental (molar) degeneration (see Chap. 37, Clinical Findings). Incomplete (partial) hydatidiform moles may be triploid or trisomic for only chromosome 16. Although these fetuses frequently abort early, the few carried longer are grossly malformed. Advanced maternal and paternal age does not increase the incidence of triploidy.

Tetraploid abortuses are rarely live born and are most often aborted early in gestation.

Chromosomal structural abnormalities infrequently cause abortion. Some infants who are live born with a balanced translocation may appear normal as discussed in Parental Chromosomal Abnormalities.

EUPLOID ABORTION

Chromosomally normal fetuses tend to abort later in gestation than those with aneuploidy. For example, although 75 percent of aneuploid abortions occurred before 8 weeks, euploid abortions peaked at about 13 weeks (Kajii, 1980). The incidence of euploid abortions increases dramatically after maternal age exceeds 35 years (Stein, 1980).

Maternal Factors

The causes of euploid abortions are poorly understood, although a variety of medical disorders, environmental conditions, and developmental abnormalities have been implicated. The well-known influence of maternal age was discussed above.

INFECTIONS

According to the American College of Obstetricians and Gynecologists (2001), infections are an uncommon cause of early abortion. Even in their study of insulin-dependent diabetic womenâ€”presumably more susceptible to infectionâ€”Simpson and co-workers (1996) found no evidence of infection-induced miscarriage.

A number of specific infections have been studied. For example, although *Brucella abortus* and *Campylobacter fetus* cause abortion in cattle, they do not do so in humans (Sauerwein, 1993). There is also no evidence that either *Listeria monocytogenes* or *Chlamydia trachomatis* stimulate abortions in humans (Feist, 1999; Osser, 1996; Paukku, 1999). In a prospective study, infection with herpes simplex virus in early pregnancy also did not increase the incidence (Brown, 1997). Evidence that *Toxoplasma gondii* causes abortion in humans remains inconclusive.

Data concerning a link between some other infections and increased abortion are conflicting. For example, Quinn and co-workers (1983a, b) provided serologic evidence that supports a role for *Mycoplasma hominis* and *Ureaplasma urealyticum* . Conversely, Temmerman and associates (1992) found no link between genital mycoplasma and spontaneous abortion. They did find abortion to be independently associated with serologic evidence of syphilis and human immunodeficiency virus (HIV)-1 infection, and with vaginal colonization with group B streptococci. In contrast, van Benthem and associates (2000) reported that women had the same risk for spontaneous abortion before and after they had developed HIV infection. Oakeshott and associates (2002) reported an association between second, but not first-trimester miscarriage, and bacterial vaginosis.

CHRONIC DEBILITATING DISEASES

Early abortions are rarely secondary to chronic wasting diseases such as tuberculosis or carcinomatosis. Celiac sprue, however, has been reported to cause both male and female infertility and recurrent abortions (Sher, 1994).

ENDOCRINE ABNORMALITIES

Hypothyroidism

Iodine deficiency may be associated with miscarriages (CastaÃ±eda, 2002). Thyroid hormone deficiency is common in women, and it is usually caused by an autoimmune disorder, but any effects of hypothyroidism on early pregnancy loss have not been adequately studied. Even without hypothyroidism, thyroid autoantibodies are associated with an increased incidence of miscarriage

(Abramson, 2001; Lakasing, 2005). As discussed in Hypothyroidism, the data are less convincing that women with recurrent miscarriage have a greater incidence of antithyroid antibodies than normal controls.

Diabetes Mellitus

Spontaneous abortion and major congenital malformation rates are both increased in women with insulin-dependent diabetes (Greene, 1999). The risk appears related to the degree of metabolic control in early pregnancy. In a prospective study, Mills and associates (1988) reported that excellent glucose control within 21 days of conception resulted in a miscarriage rate similar to that in nondiabetic controls. Poor glucose control, however, resulted in a markedly increased abortion rate. Overt diabetes is a cause of recurrent pregnancy loss, and Craig and co-workers (2002) have reported a higher incidence of insulin resistance in those with recurrent miscarriage. This is discussed further in Diabetes Mellitus.

NUTRITION

Dietary deficiency of any one nutrient or moderate deficiency of all nutrients does not appear to be an important cause of abortion. Even hyperemesis gravidarum during early pregnancy with significant weight loss is rarely followed by miscarriage.

DRUG USE AND ENVIRONMENTAL FACTORS

A variety of different agents have been reported to be associated with an increased incidence of abortion.

Tobacco

Smoking has been linked with an increased risk for euploid abortion (Kline, 1980). Two studies suggested that the abortion risk increases in a linear fashion with the number of cigarettes smoked per day (Armstrong, 1992; Chatenoud, 1998). Two subsequent studies, however, failed to support this association (Rasch, 2003; Wisborg, 2003).

Alcohol

Both spontaneous abortion and fetal anomalies may result from frequent alcohol use during the first 8 weeks of pregnancy (Floyd, 1999). The risk seems to be related to both frequency and dose (Armstrong, 1992; Kline, 1980). A low level of alcohol consumption during pregnancy was not associated with a significant risk for abortion (Cavallo, 1995; Kesmodel, 2002).

Caffeine

Armstrong and associates (1992) reported that women who consumed at least five cups of coffee per day had a slightly increased abortion risk, and that above this threshold, the risk correlated linearly. Similarly, Cnattingius and colleagues (2000) observed a significantly increased abortion risk only in women who consumed at least 500 mg of caffeine dailyâ€”roughly equivalent to 5 cups of coffee. Klebanoff and associates (1999) reported that pregnant women in whom levels of the caffeine metabolite, paraxanthine, were extremely elevated had a twofold risk for miscarriage. They concluded that moderate caffeine consumption was unlikely to cause spontaneous abortion.

Radiation

In therapeutic doses given to treat malignancy, radiation is certainly an abortifacient. Although lower doses are less toxic, the human dose to effect abortion is not precisely known. According to Brent (1999), exposure to less than 5 rads does not increase the risk for miscarriage.

Contraceptives

Oral contraceptives or spermicidal agents used in contraceptive creams and jellies are not associated with an increased miscarriage rate. When intrauterine devices fail to prevent pregnancy, however, the risk of abortion, and specifically septic abortion, increases substantively (see Chap. 5, Pregnancy with Retained IUD).

Environmental Toxins

Accurately assessing the relationship between environmental exposures and miscarriage poses challenges. There may be difficulties in measuring the intensity and duration of exposure, and there is little information to conclusively indict or absolve any specific agent. Nevertheless, it seems prudent to limit exposure of pregnant women to environmental toxins.

Some studies include those by Barlow and Sullivan (1982) who found that arsenic, lead, formaldehyde, benzene, and ethylene oxide possibly cause miscarriages. Video display terminals and exposure to their accompanying electromagnetic fields do not adversely affect miscarriage rates (Schnorr, 1991). Similarly, no effects were found with occupational exposure to ultrasound (Taskinen, 1990). An increased risk of miscarriage has been described for dental assistants exposed to 3 or more hours of nitrous oxide per day in offices without gas-scavenging equipment, but not in offices using such equipment (Rowland, 1995). Before the use of such equipment, Boivin (1997) concluded that women occupationally exposed to anesthetic gases had an increased risk for miscarriage. In another meta-analysis, Dranitsaris and colleagues (2005) identified a small incremental risk for spontaneous abortion in female staff who worked with cytoxic chemotherapeutic drugs.

IMMUNOLOGIC FACTORS

A number of immune-mediated disorders are associated with early pregnancy loss. Many tend to be repetitive, and they are considered with recurrent miscarriage (Immunologic Factors).

INHERITED THROMBOPHILIAS

There are a number of genetic disorders of blood coagulation that may increase the risk of both arterial and venous thrombosis. Some of the better studied thrombophilias are caused by mutations of the gene for factor V Leiden, prothrombin, antithrombin, proteins C and S, and methylene tetrahydrofolate reductase (hyperhomocysteinemia). Because these are most commonly associated with recurrent miscarriage, they are considered in detail in Inherited Thrombophilias.

MATERNAL SURGERY

Uncomplicated abdominal or pelvic surgery performed during early pregnancy does not appear to increase the risk for abortion. Ovarian tumors are generally removed without interfering with pregnancy. An important exception involves early removal of the corpus luteum cyst or the ovary in which the corpus luteum resides. If performed prior to 10 weeks' gestation, supplemental progesterone is indicated. If between 8 and 10 weeks, then only one injection of intramuscular 17-hydroxyprogesterone caproate, 150 mg, is required immediately after surgery. If the corpus luteum is excised between 6 and 8 weeks, then two additional doses should be given 1 and 2 weeks after the first.

TRAUMA

Presumably, major abdominal trauma can precipitate abortion, however, this is unusual in early pregnancy. Any effects of minor trauma on abortion rates is difficult to ascertain. Minor trauma without pregnancy complication is often forgotten, whereas minor trauma temporally associated with miscarriage is more likely to be recalled. In general, trauma contributes minimally to the incidence of abortion.

UTERINE DEFECTS

Acquired Uterine Defects

Large and multiple uterine leiomyomas are common, and they may cause miscarriage. In most instances, their location is more important than their size (see Chap. 9, Infertility and Pregnancy Wastage). Uterine synechiaeâ€"known as *Asherman syndrome* â€"usually result from destruction of large areas of endometrium by curettage. A hysterosalpingogram may show characteristic multiple filling defects, but hysteroscopy is more accurate (Figs. 19-5, and 41-41.1) (Raziel, 1994). With subsequent pregnancy, the amount of remaining endometrium may be insufficient to support the pregnancy, and abortion may ensue. Treatment is discussed in Chapter 20, Intrauterine Adhesions.

Developmental Uterine Defects

Abnormal mÃ¼llerian duct formation or fusion defects may develop spontaneously or may follow in utero exposure to diethylstilbestrol (see Chap. 18, Diethylstilbestrol-Induced Reproductive Tract Abnormalities). Although they can cause midpregnancy loss and other preterm birth and pregnancy complications, it is controversial whether uterine defects cause early miscarriage. As discussed in Anatomic Factors, corrective procedures to prevent abortion, if done at all, should be performed as a last resort, with a full understanding that they may lack efficacy (American College of Obstetricians and Gynecologists, 2001).

Incompetent Cervix

This describes a discrete obstetric entity characterized by painless cervical dilatation in the second trimester. It can be followed by prolapse and ballooning of membranes into the vagina, and ultimately expulsion of an immature fetus. Chasen and associates (2005) reported that a prior dilatation and evacuation (D&E) or dilatation and extraction (D&X) after 20 weeks does not increase the chances of an incompetent cervix. This condition is discussed in detail in Chapter 9 of *Williams Obstetrics* (Cunningham, 2005).

Paternal Factors

Little is known about paternal factors in the genesis of miscarriage. Certainly, chromosomal abnormalities in sperm have been associated with abortion (Carrell, 2003).

Clinical Classification of Spontaneous Abortion

The clinical aspects of spontaneous abortion can be classified a number of ways. Commonly used subgroups include threatened, inevitable, incomplete, and missed abortion. If the products of conception and pelvic organs are infected, septic abortion is diagnosed. Finally, recurrent miscarriageâ€"also termed recurrent pregnancy lossâ€"describes consecutive early losses with implied similar etiology.

THREATENED ABORTION

The clinical diagnosis of threatened abortion is presumed when a bloody vaginal discharge or bleeding appears through a closed cervical os during the first half of pregnancy. Vaginal spotting or heavier bleeding develops in 20 to 25 percent of women during early gestation and it may persist for days or weeks. Approximately half of these pregnancies will abort, although the risk is substantially lower if fetal cardiac activity can be documented (Tongsong, 1995). Eddleman and associates (2006) designed an individualized risk assessment model for spontaneous pregnancy loss in over 35,000 pregnancies. By far, bleeding during the current pregnancy was the most predictive risk factor for pregnancy loss. Even if abortion does not follow early bleeding, these fetuses are at increased risk for preterm delivery, low birthweight, and perinatal death (Johns, 2006; Weiss, 2002). Fortunately, the risk of a malformed surviving infant does not appear to be increased. There are also maternal risks that include antepartum hemorrhage, manual removal of the placenta, and cesarean delivery (Wijesiriwardana, 2006).

Some bleeding near the time of expected menses may be physiologic. Cervical lesions commonly bleed in early pregnancy, especially after intercourse. Polyps presenting at the external cervical os and decidual reaction in the cervix also tend to bleed in early gestation. Bleeding from these benign sources is not accompanied by lower abdominal pain and low backache.

With miscarriage, bleeding usually begins first, and cramping abdominal pain follows a few hours to several days later. The pain may present variablyâ€"as anterior and clearly rhythmic cramps; as a persistent low backache, associated with a feeling of pelvic pressure; or as a dull, midline, suprapubic discomfort. Whichever form the pain takes, the combination of bleeding and pain predicts a poor prognosis for pregnancy continuation.

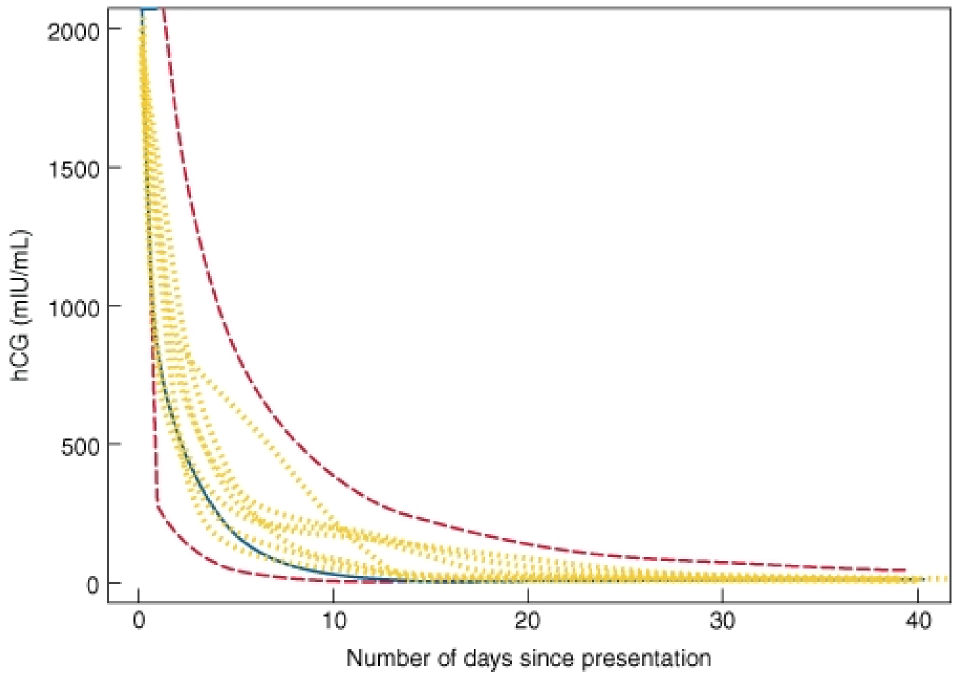
Because ectopic pregnancy, ovarian torsion, and the other types of abortion may mimic threatened abortion, the threshold to examine women with vaginal bleeding and pain should be low. If bleeding is persistent or heavy, a hematocrit should be performed. If blood loss is sufficient to cause significant anemia or hypovolemia, pregnancy evacuation is usually indicated.

There are no effective therapies for threatened abortion. Bedrest, although often prescribed, does not alter its course. Acetaminophen-based analgesia may be given to help relieve discomfort. As discussed in Chapter 7, Differential Diagnosis, transvaginal sonography, serial serum quantitative β-hCG and serum progesterone levels, used alone or in combination, can help to ascertain if a fetus is alive and within the uterus. None of these tests in early gestation are 100-percent accurate to confirm fetal death, thus subsequent evaluations over a week or two may be necessary. **Ectopic pregnancy should always be considered in the differential diagnosis of threatened abortion** . In one report, Condous and colleagues (2005) described 152 women with heavy bleeding who were diagnosed to have a completed miscarriage and an endometrial thickness <15 mm. Almost 6 percent of these women were found to have an ectopic pregnancy on further evaluation.

It is imperative to recognize an early ectopic pregnancy before tubal rupture develops. For women with abnormal bleeding or pelvic pain who have low levels of β-hCG detectable in serum, attempts are made to differentiate an extrauterine pregnancy from a normal uterine pregnancy or an early miscarriage. Barnhart and colleagues (2004a) have provided data concerning composite

serum β-hCG disappearance curves in women with early miscarriage (Fig. 6-2). This same group has provided similar data for symptomatic women with early pregnancies who go on to have a normal pregnancy (Barnhart, 2004b).

FIGURE 6-2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Composite curve describing decline in serial human chorionic gonadotropin (hCG) values starting at a level of 2000 mIU/mL following early spontaneous miscarriage. The light dotted lines represent actual curves from subjects. The solid line is the predicted curve based on the summary of all data. The two hatched dark lines represent the 95-percent confidence interval of the predicted curve. *(From Barnhart, 2004a, with permission.)*

ANTI-D IMMUNOGLOBULIN

Treatment of D-negative women with anti-D immunoglobulin is recommended following miscarriage because up to 5 percent of D-negative women will become isoimmunized without it. This practice is controversial with threatened abortion because it lacks evidence-based support (American College of Obstetricians and Gynecologists, 1999; Weissman, 2002).

INEVITABLE ABORTION

Gross rupture of the membranes, evidenced by leaking amnionic fluid, in the presence of cervical dilatation signals almost certain abortion. Commonly, either uterine contractions begin promptly, resulting in miscarriage, or infection develops. Rarely, a gush of fluid from the uterus during the first half of pregnancy is without serious consequence. The fluid may have collected previously between the amnion and chorion. Because of this possibility, if a sudden discharge of fluid in early pregnancy occurs before pain, fever, or bleeding, then diminished activity with observation is reasonable. If after 48 hours no additional amnionic fluid has escaped and if there is no bleeding, pain, or fever, a woman may resume her usual activities except for any form of vaginal penetration. If, however, the gush of fluid is accompanied or followed by bleeding, pain, or fever, then abortion should be considered inevitable, and the uterus emptied.

INCOMPLETE ABORTION

Bleeding ensues when the placenta, in whole or in part, detaches from the uterus. During incomplete abortion, the internal cervical os opens and allows passage of blood. The fetus and placenta may remain entirely in utero or may partially extrude through the

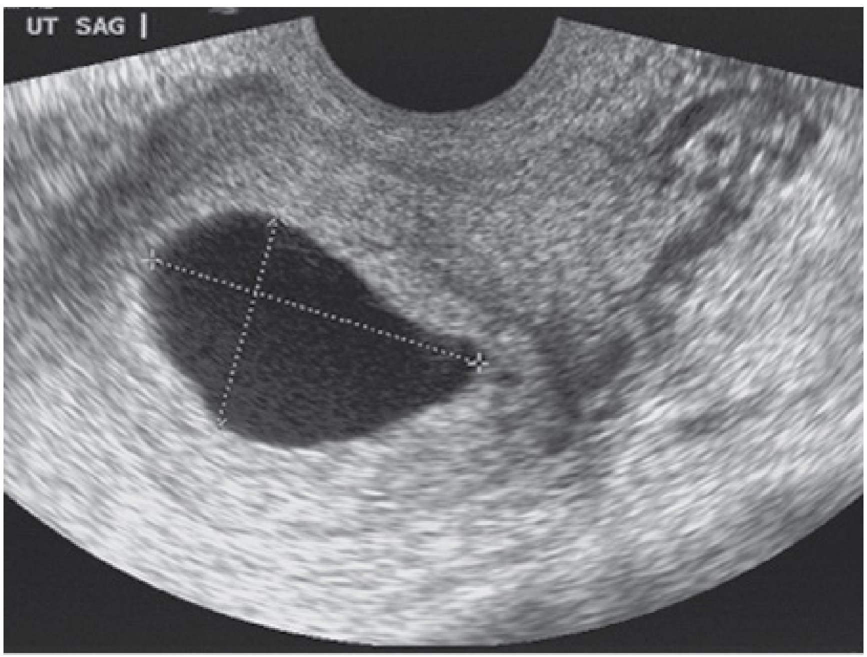
dilated os. Before 10 weeks, the fetus and placenta are commonly expelled together, but later they are delivered separately. In some women, additional cervical dilatation is necessary before curettage is performed. In many cases, retained placental tissue simply lies loosely in the cervical canal, allowing easy extraction from an exposed external os with ring forceps. Suction curettage, as described later, effectively evacuates the uterus. In clinically stable women, expectant management can also be a reasonable option (Blohm, 2005).

Hemorrhage from incomplete abortion of a more advanced pregnancy is occasionally severe but rarely fatal. Therefore, in women with more advanced pregnancies or with heavy bleeding, evacuation is promptly performed. If there is fever, appropriate antibiotics are given before curettage.

MISSED ABORTIONÂ€”EARLY PREGNANCY FAILURE

The term *missed abortion* is contemporaneously imprecise because it was defined many decades before the advent of immunologic pregnancy tests and sonography (Fig. 6-3). It was used to describe dead products of conception that were retained for days, weeks, or even months in the uterus with a closed cervical os. Because spontaneous miscarriages are almost always preceded by embryofetal death, most were correctly referred to as "missed". In the typical instance, early pregnancy appears to be normal. Characteristically, amenorrhea, nausea and vomiting, breast changes, and uterine growth are present. After embryonic death, there may or may not be vaginal bleeding or other symptoms of threatened abortion.

FIGURE 6-3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Transvaginal sonography displays anembryonic gestation. *(Courtesy of Dr. Elysia Moschos.)*

Because technology now allows identification of fetal or embryonic death at this early stage, most women choose medical or surgical termination at the time of discovery. If the pregnancy is not terminated, and if miscarriage does not follow for days or weeks, then uterine size remains unchanged, and then gradually becomes smaller. Mammary changes usually regress, and women often lose a few pounds. Many women have no symptoms during this period except persistent amenorrhea. If the missed abortion terminates spontaneously, and most do, the process of expulsion is the same as in any abortion.

SEPTIC ABORTION

In the past septic abortion and maternal deaths associated with criminal abortions were common, but currently are rare. That said, miscarriage and elective abortion are occasionally complicated by severe and even fatal infections (Barrett, 2002). Uterine infection is the most common manifestation of postabortal sepsis, but parametritis, peritonitis, septicemia, and even endocarditis, occasionally develop (Vartian, 1991). Treatment of infection includes prompt administration of intravenous broad-spectrum antibiotics followed by uterine evacuation (see Chap. 3, Treatment). With severe sepsis syndrome, acute respiratory distress syndrome or disseminated intravascular coagulopathy may develop, and supportive care is essential.

In mid-2005, the Centers for Disease Control and Prevention (2005) reported four deaths associated with medical abortion that were caused by toxic shock syndrome and *Clostridium sordellii* infection. Fischer and colleagues (2005) detailed these infections and described clinical manifestations that began within 1 week after the medically induced abortion. The hallmark was severe endothelial injury with capillary leakage and hemoconcentration, hypotension, and profound leukocytosis. As emphasized by Greene (2005), these infections are rare events but bear close surveillance.

Management

With death of the conceptus now easy to verify with current sonographic technology, management can be more individualized. Expectant, medical, and surgical management are all reasonable options unless there is serious bleeding or infection. Surgical treatment is definitive and predictable, but is invasive and not necessary for all women. Expectant and medical management may obviate curettage, but are associated with unpredictable bleeding, and some women will need unscheduled surgery. For example, in the observational study of Luise and colleagues (2002), 81 percent of almost 1,100 women with suspected first-trimester miscarriage reported spontaneous resolution.

A number of randomized studies have been done to evaluate these methods. In many cases, however, the studies themselves are not comparable because different criteria were used for inclusion, and various techniques were employed. For example, if there is vaginal bleeding, then medical therapy for early pregnancy failure is enhanced (Creinin, 2006). Some of these studies are listed in Table 6-2. A number of generalizations can be made:

1. Success is dependent on the type of early pregnancy failure.
2. With spontaneous incomplete abortion, expectant management results in spontaneous completion in about 80 percent of cases. It is likely that treatment with prostaglandin E_1 (PGE_1) increases this rate only slightly.
3. For early pregnancy failure, otherwise not further defined, PGE_1 given orally or vaginally is effective for completed abortion by 7 days in about 85 percent.
4. Curettage is a quick resolution that is almost 100 percent successful in completing early pregnancy failures.

Table 6-2 Randomized Controlled Studies for Management of Early Pregnancy Loss

Study	Type of Abortion	No.	Treatment Arms	Outcomes
Nielsen (1995)	SAB incomplete	103	(1) Expectant	80% completed at 3 days; bled mean of 1 day longer
		52	(2) Curettage	
Nielsen (1999)	SAB incomplete	62	(1) Mifepristone 400 µg orally + PGE_1 , 600 µg at 48 hrs	82% completed at 5d
		60	(2) Expectant	76% completed at 5 d
Blohm (2005)	"Signs of miscarriage"	126	(1) Placebo	54% completed at 7 days
			(2) PGE_1 , 400 µg vaginally	81% completed at 7 days; more pain, required more analgesia

Lister (2005)	Pregnancy failure[a]	36	(1) Placebo	40% curettage rate
			(2) PGE_1 , 800 µg vaginally	12% curettage rate
Nguyen (2005)	SAB incomplete	149	(1) PGE_1 , 600 µg orally	60% completed at 3 days; 95% at 7 days; 3% curettage
		145	(2) PGE_1 , 600 µg orally + 600 mg orally at 4 hrs	
Zhang (2005)	Pregnancy failure[b]	652	(1) PGE_1 , 800 µg vaginally	71% completed at 3 days; 84% by 8 days; 16% failure rate
			(2) Vacuum aspiration	97% successful; 3% failure rate

SAB = spontaneous abortion; PGE = prostaglandin E.

[a] Includes anembryonic gestation, embryonic or fetal death, without signs of incomplete SAB.

[b] Includes anembryonic gestation, embryonic or fetal death, or incomplete or inevitable SAB.

Thus, there are several management options that can be selected by the woman and her gynecologist. Of course, with dangerous hemorrhage or infection, prompt completion of abortionâ€"either medically or surgicallyâ€"is warranted.

RECURRENT PREGNANCY LOSS

Also known as *recurrent spontaneous abortion* and *recurrent pregnancy loss* , recurrent miscarriage is classically defined as three or more consecutive pregnancy losses at 20 weeks' gestation or less or with fetal weights less than 500 g. Most women with recurrent miscarriage have embryonic or early fetal loss, with recurrent losses after 14 weeks being much less common (Stephenson, 2007). Although the formal definition includes three or more miscarriages, many agree that an evaluation should be performed, or at least considered, following two consecutive losses. This is because the risk of subsequent loss after two successive miscarriages is similar to that following three lossesâ€"approximately 30 percent (Harger, 1983). Remarkably, as shown in Table 6-3, the chance of successful pregnancy may approach 50 percent even after six losses (Poland, 1977; Warburton, 1964).

Table 6-3 Recurrent Risk for Spontaneous Abortion Following Up to Six Losses

	No. Prior SABs	% Risk
Prior liveborn	0	12
	1	24
	2	26
	3	32
	4	26
	6	53
No prior liveborn	1	19
	2	35

	3	47
	4	54

SAB = spontaneous abortion.

Data from Poland, 1977, and Warburton, 1964, with permission.

Recurrent miscarriage should be distinguished from sporadic pregnancy loss described in the previous section. Sporadic loss implies that intervening pregnancies have resulted in healthy infants. Others distinguish *primary recurrent miscarriage* â€"no successful pregnanciesâ€"from *secondary recurrent miscarriage* â€"one prior live birth. The latter group does not reach a risk of subsequent loss of 32 percent until after three miscarriages. Thus, it is reasonable to delay evaluation of secondary recurrent pregnancy loss until there have been three losses (Poland, 1977).

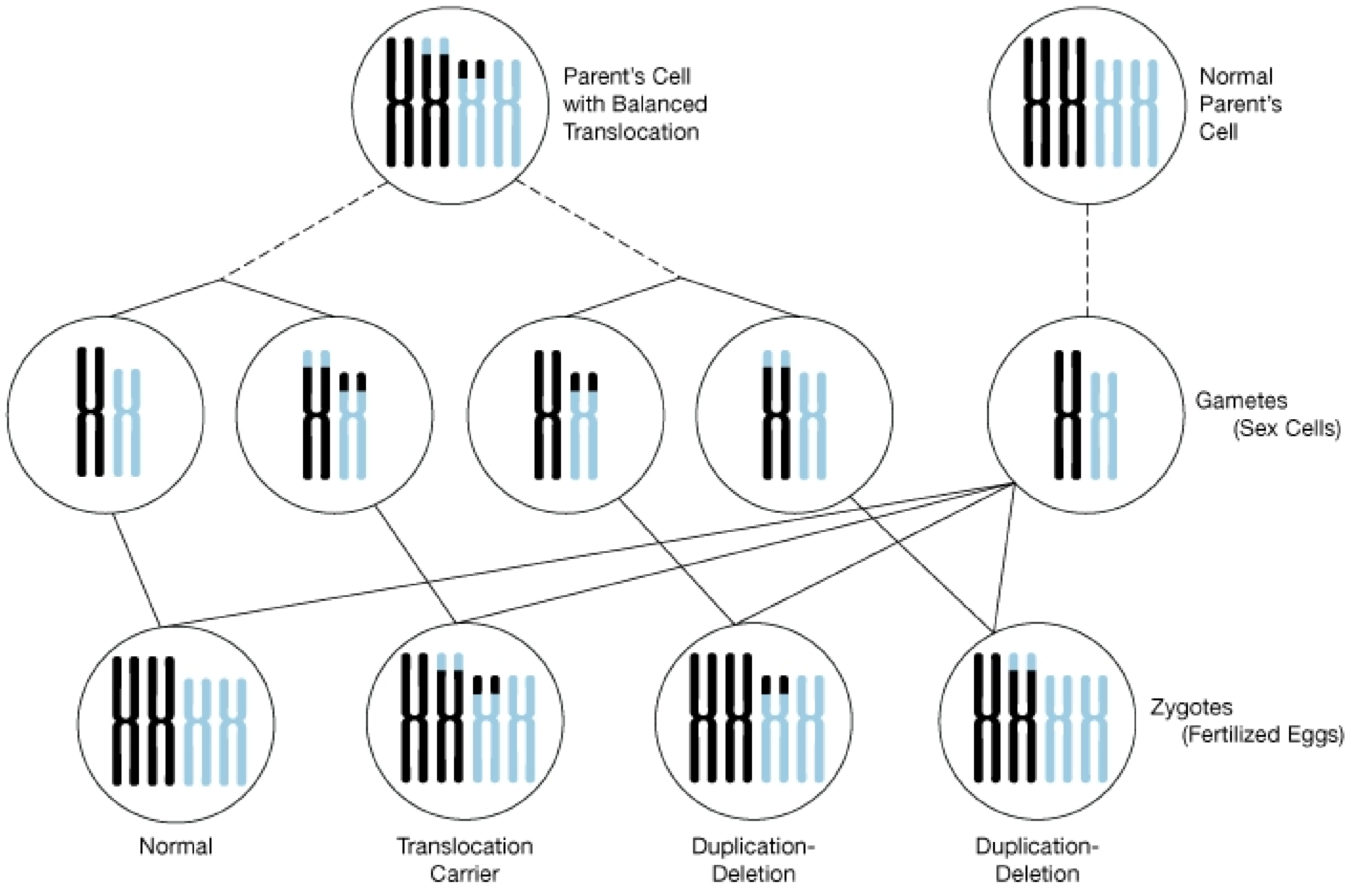
The causes of recurrent miscarriage parallel those of sporadic miscarriage, although the relative incidence differs between the two categories (Reddy, 2007). For example, first-trimester losses with recurrent miscarriage have a significantly lower incidence of genetic anomalies (Sullivan, 2004). In one series, normal karyotypes were identified in half of recurrent miscarriages but only a fourth of sporadic losses. The timing of the pregnancy losses may provide a clue to their cause. By way of another example, genetic factors most frequently result in early embryonic losses, whereas autoimmune or anatomic abnormalities are more likely to result in second-trimester losses (Schust, 2002).

Parental Chromosomal Abnormalities

Although these account for only 2 to 4 percent of recurrent losses, karyotypic evaluation of both parents remains a critical part of evaluation. Therapel and colleagues (1985) summarized data from 79 studies of couples with two or more miscarriages. These included 8208 women and 7834 men, and chromosomal abnormalities were detected in 2.9 percentâ€"a fivefold greater incidence than that observed in the general population. The male: female gender ratio of abnormalities was about 2:1. Balanced reciprocal translocations accounted for 50 percent of identified abnormalities; Robertsonian translocations for 24 percent; X chromosome mosaicism such as 47, XXY for 12 percent; and inversions and a variety of other anomalies comprised the remainder.

If one parent carries a balanced translocation, the karyotype of the resultant pregnancy may be normal, the same balanced translocation, or an unbalanced translocation (Fig. 6-4). Balanced translocations are likely to cause subsequent recurrent miscarriage in the offspring. An unbalanced translocation may produce either a miscarriage, fetal anomaly, or stillborn.

FIGURE 6-4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Gametes produced by a balanced translocation carrier.

The prognosis for these couples, however, is good. Franssen and colleagues (2006) studied 247 couples with a balanced translocation and reported that although they had an increased miscarriage rate compared with noncarriers, almost 85 percent had at least one healthy infant. Thus, a history of second- trimester loss or fetal anomaly should raise the suspicion that an abnormal chromosome pattern is present in one parent. All couples with an abnormal karyotype should be offered preimplantation genetic counseling.

Some recommend that fetal tissue be routinely studied for chromosomal analysis following a second consecutive miscarriage (Stephenson, 2006). One reason cited is that an abnormal karyotype suggests a sporadic loss, and therefore does not predict increased risk for the next pregnancy. Conversely, an abortus with a normal karyotype might suggest an alternative cause for the pregnancy loss and imply the need for earlier evaluation.

Opponents of routine analysis cite the extreme expense. They note that it should be presumed that a woman with recurrent miscarriages has the same risk of an aneuploid abortion as any other womanâ€”about 50 percent (see Table 6-1). Moreover, karyotyping of products of conception may actually be misleading. In many cases, cells cannot be grown in culture because of embryonic tissue death. As a general rule, tissue obtained by curettage is more likely to grow in culture. Also, detection of a 46, XX karyotype may simply reflect contamination with maternal tissues. And many conceptions are chromosomal mosaics of which a significant proportion will develop into phenotypically and functionally normal neonates. This is particularly true if the abnormal cells are from *placental mosaicism* . Finally, karyotypically normal cells are likely to have a growth advantage in culture.

For all of these reasons, karyotyping of products of conception may not accurately reflect fetal karyotype. Because of the expense

and limited information provided, we do not recommend routine karyotyping of pregnancy products.

Anatomic Factors

A number of anatomic abnormalities of the genital tract have been implicated in recurrent miscarriage. According to Devi Wold and colleagues (2006), 15 percent of women with three or more consecutive miscarriages have a congenital or acquired uterine anomaly. These essentially are the same as those associated with all miscarriages and are discussed in Developmental Uterine Defects. They include acquired uterine abnormalities such as intrauterine synechiaeâ€"Asherman syndrome, leiomyoma, endometrial polyp, and cervical incompetence. Developmental defects include septate, bicornuate, and unicornuate uterus, as well as uterine didelphys. Also, reproductive-tract abnormalities may be associated with in utero exposure to diethylstilbestrol and include a small uterine cavity and incompetent cervix. The frequency of these anomalies in women with recurrent miscarriage varies widely depending on testing used and criteria set for abnormality.

Salim and colleagues (2003) described nearly 2,500 women who were screened for developmental uterine anomalies using three-dimensional sonography. Anomalies were identified in 24 percent of women with recurrent miscarriage, but only 5 percent of normal controls without recurrent miscarriage. In other studies, the prevalence of uterine anomalies has been estimated to be only 7 to 15 percent in women with repetitive losses (Ashton, 1988; Makino, 1992).

TREATMENT

As discussed in Developmental Uterine Defects, the evidence is not robust to link these anatomic anomalies with early pregnancy loss. It is therefore difficult to prove that their correction improves pregnancy outcome (American College of Obstetricians and Gynecologists, 2001). That said, Saygili-Yilmaz and colleagues (2003) retrospectively reviewed pregnancy outcomes following hysteroscopic metroplasty in women who had a septate uterus and more than two prior miscarriages. In 59 such women, the incidence of miscarriage decreased from 96 to 10 percent following surgery, and term pregnancies increased from none to 70 percent. In another study, Saygili-Yilmaz and associates (2002) reported that the miscarriage rate of 65 percent with a septum decreased to 15 percent after hysteroscopic resection. A further discussion of treatment outcome is found in Chapter 18, Diagnosis and Treatment.

In another retrospective review, Katz and colleagues evaluated 90 women with uterine synechiae who had at least two prior miscarriages or preterm perinatal deaths or both. With adhesiolysis, miscarriage rates decreased from 79 to 22 percent and term pregnancies increased from 18 to 69 percent. Other studies have reported similar outcomes with prognosis correlating to the severity of the disease (Al-Inany, 2001; Goldenberg, 1995; Katz, 1996). Directed hysteroscopic lysis of adhesions is preferable to curettage (see Section 41-41, Lysis of Intrauterine Adhesions).

As described in Chapter 9, Infertility and Pregnancy Wastage, it is controversial whether submucous myomas cause recurrent miscarriage more than infrequently. If symptomatic, most agree that submucosal and intracavitary fibroids should be excised. In recent studies of women undergoing in vitro fertilization, pregnancy outcomes were adversely affected by submucosal myomas, but not by those that were subserosal or intramural and less than 5 to 7 cm (Jun, 2001; Ramzy, 1998).

Immunologic Factors

Much attention has focused on the immune system as important in recurrent pregnancy loss. In their analysis of published studies, Yetman and Kutteh (1996) determined that 15 percent of more than 1,000 women with recurrent miscarriage had recognized autoimmune factors. Two primary pathophysiologic models are the *autoimmune theory* , immunity against self, and the *alloimmune theory* , immunity against another person.

AUTOIMMUNE FACTORS

Miscarriages are more common in women with systemic lupus erythematosus (Warren, 2004). Many of these women have antiphospholipid antibodies, which are a family of autoantibodies that bind to negatively charged phospholipids, phospholipid-binding proteins, or a combination of the two (Branch, 2003). They also are found in women without lupus. Indeed, in up to 5 percent of normal pregnant women, lupus anticoagulant (LAC) and anticardiolipin antibody (ACA) have been linked with excessive pregnancy wastage. Instead of causing miscarriage, they more likely are found with fetal death after midpregnancy. Because of this, fetal death is one criterion for diagnosis of the *antiphospholipid syndrome* (Lakasing, 2005).

Antiphospholipid Antibody Syndrome

Diagnosis of this syndrome requires at least one of each clinical and laboratory criterion (American College of Obstetricians and Gynecologists, 2005a). These are listed in Table 6-4. Screening tests for lupus anticoagulant vary by institution, but include a number of suitable tests.

Table 6-4 Clinical and Laboratory Criteria for Diagnosis of Antiphospholipid Antibody Syndrome[a]

Clinical criteria 1. Three or more consecutive spontaneous abortions before 10 weeks (recurrent pregnancy loss); delivery before 34 weeks; one or more unexplained fetal deaths of a morphologically normal infant; or severe preeclampsia or placental insufficiency necessitating delivery before 34 weeks. 2. Arterial or vascular thrombosis without an obvious precipitating cause; small-vessel thrombosis in any tissue or organ, without significant evidence of vasculitis.
Laboratory criteria 1. Moderate to high levels of IgG or IgM anticardiolipin antibodies. 2. Detection of lupus anticoagulant. These tests must be positive on at least two occasions at least 6 weeks apart.

IgG = immunoglobulin G; IgM = immunoglobulin M.

[a] At least one clinical and laboratory criterion each must be present for diagnosis.

Antiphospholipid antibodies are the only autoimmune condition that can be correlated with adverse pregnancy outcome. They have been proposed to cause fetal loss because these antibodies inhibit release of prostacyclin, a potent vasodilator and inhibitor of platelet aggregation. In contrast, platelets produce thromboxane A_2 which is a vasoconstrictor that also promotes platelet aggregation. These autoantibodies have also been shown to inhibit protein C activation, which results in coagulation and fibrin C formation. Clinically, these events that lead to hypercoagulability and recurrent thrombosis within the placenta.

Women with both a history of early fetal loss and high levels of these antibodies may have a 70 percent miscarriage recurrence (Dudley and Branch, 1991). In a prospective study of 860 women screened for anticardiolipin antibody in the first trimester, Yasuda and colleagues (1995) reported that 7 percent tested positive. Miscarriage developed in 25 percent of the antibody-positive group, compared with only 10 percent of the negative group. In another study, however, Simpson and associates (1998) found no association between early pregnancy loss and the presence of either anticardiolipin antibody or lupus anticoagulant.

Treatment

There are treatment regimens for antiphospholipid syndrome that increase live birth rates. Two randomized trials support that treatment with a combination of heparin plus low-dose aspirin can improve the live birth rate compared with low-dose aspirin alone. Kutteh (1996) randomized 50 such women to receive either low-dose aspirin alone or low-dose aspirin plus heparin. Women who received both aspirin and heparin had significantly more viable infantsâ€”80 versus 44 percent, respectively. Rai and colleagues (1997) reported a 77-percent live birth rate with low-dose aspirin plus low-dose heparin therapyâ€”5000 units twice dailyâ€"versus 42 percent with aspirin alone. In contrast, Farquharson and associates (2002) observed a 72-percent live birth rate using low-dose aspirin alone versus a 78-percent rate using low-dose aspirin plus low-dose low-molecular-weight heparin.

As emphasized by Branch and Khamashta (2003), the discrepant reports are confusing, and therapeutic guidelines are blurred. Because of this, we individualize therapy for women who meet the criteria for antiphospholipid syndrome and involve them in the decision-making process. We recommend a regimen proposed by the American College of Obstetricians and Gynecologists (2005a). We give low-dose aspirinâ€"81 mg orally per day, along with unfractionated heparinâ€"5,000 units subcutaneously, twice daily. This therapy, begun when pregnancy is diagnosed, is continued until delivery. Although this treatment may improve overall pregnancy success, these women remain at high risk for preterm labor, premature rupture of membranes, fetal growth restriction, preeclampsia, and placental abruption (Backos, 1999; Rai, 1997).

In addition to IgG and IgM anticardiolipin antibodies, there are antibody idiotypes directed to a large number of lipids (Bick, 2006).

Their measurement is expensive, frequently poorly controlled, and of uncertain relevance in the diagnosis of recurrent miscarriage. Results are likewise inconclusive regarding testing for other antibodies including rheumatoid factor, antinuclear antibodies, and antithyroid antibodies.

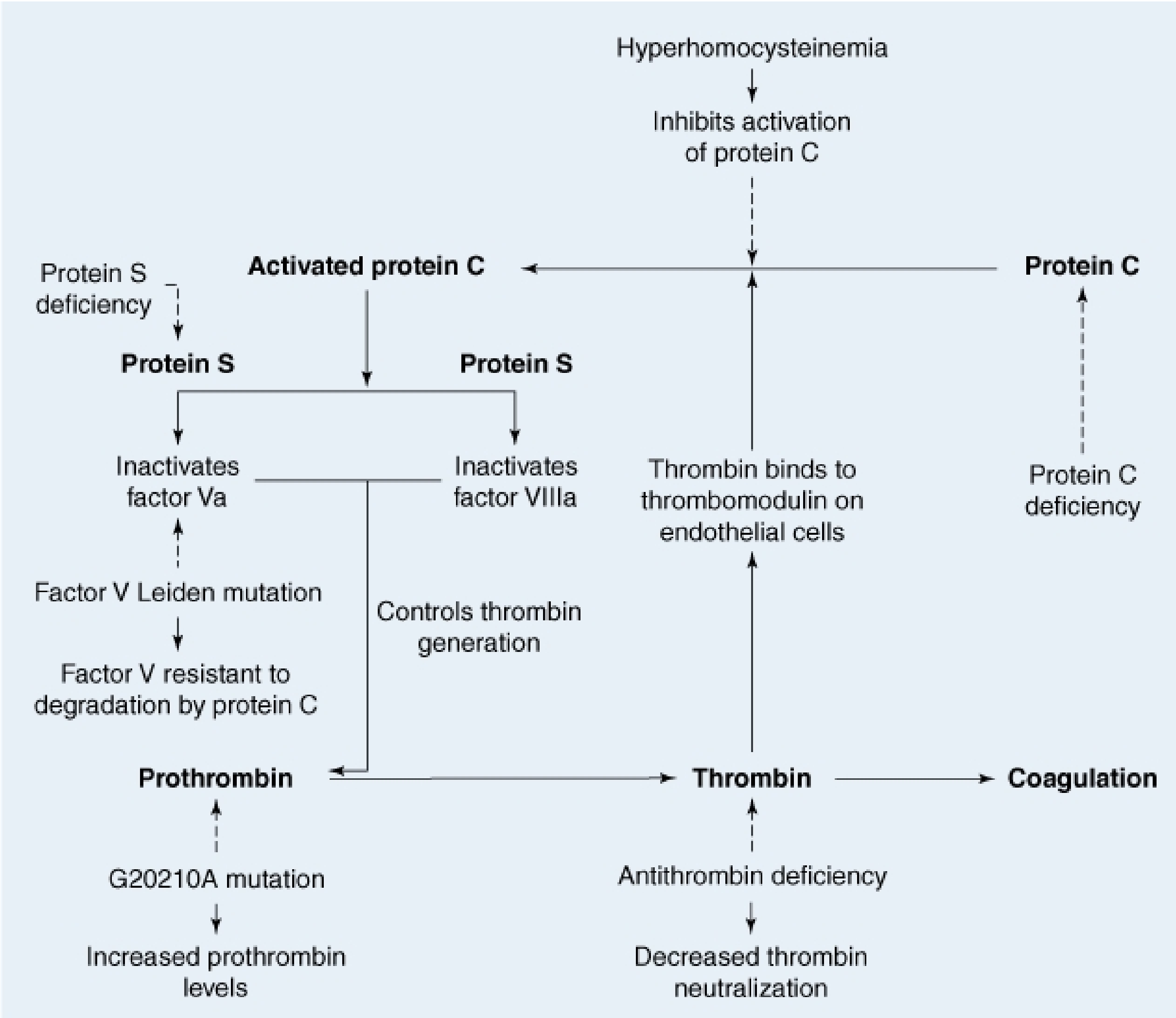
ALLOIMMUNE FACTORS

A current and attractive theory suggests that normal pregnancy requires the formation of blocking factors that prevent maternal rejection of foreign fetal antigens that have been derived from the father. A woman will fail to produce these serum blocking factors if she shares human leukocyte antigens (HLAs) with her husband. Additional alloimmune disorders have been posited to cause recurrent miscarriage, including altered natural killer (NK) cell activity and increased lymphocytotoxic antibodies. A variety of therapies to correct these disorders has been suggested, including the use of paternal-cell immunization, third-party donor leukocytes, trophoblast-membrane infusion, and intravenous immunoglobulin. None of these has withstood rigorous scrutiny, some are potentially harmful, and thus we agree with Scott (2003) and Reddy (2007) that immunotherapy cannot be recommended.

Inherited Thrombophilias

Pathologic thrombosis results from an imbalance between clotting and anticoagulation pathways. In Fig. 6-5, the clotting cascade and some of the better described thrombophilic mutations are shown. Activation of *protein S* synergizes with activated *protein C* , thereby inhibiting the actions of clotting factors V and VIII. Thus, proteins S and C have an anticoagulant effect. Decreased action of these proteins has been postulated to increase the risk for pregnancy loss. Mutation in the gene encoding factor V results in a protein that is resistant to the effects of activated protein C (aPC). The most common of a variety of mutations is at position 506 with a glutamine substitution for arginineâ€”this FV:R506Q mutation is called the *factor V Leiden mutation* . The mutation results in a protein resistant to the effects of aPC. The net result is increased factor Vâ€“induced cleavage of prothrombin to thrombin, which causes excessive coagulability. Inherited decreased or absent *antithrombin III* activity will lead to increased thrombin formation and clotting. Mutation of the *prothrombin gene* will also result in hypercoagulability. The impact of *fibrinolytic defects* on recurrent miscarriage appears to be negligible (Sotiriadis, 2007).

FIGURE 6-5



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Overview of inherited thrombophilias and their effects on the coagulation cascade.

A mutation in the gene for *methylene tetrahydrofolate reductase* causes elevated serum levels of homocysteine, which are associated with thrombosis and premature vascular disease. Hyperhomocysteinemia may also be inherited or acquired due to folic acid deficiency. In one study, elevated homocysteine levels were identified in 21 percent of women with recurrent miscarriage (Wouters, 1993)

Carp and associates (2002) and Adelberg and Kuller (2002) cast doubt on the importance of inherited thrombophilias in early miscarriage. As placental perfusion is minimal in very early pregnancy, thrombophilias may have greater clinical implications in later pregnancy. In a meta-analysis of 31 studies by Rey and colleagues (2003), recurrent miscarriage was most closely associated with the factor V Leiden and prothrombin gene mutation. Therefore, it may be reasonable to test for these mutations first in a woman with otherwise unexplained recurrent miscarriage. Treatment for the thrombophilias remains controversial, but may include heparin and aspirin. The subject was recently reviewed by Kutteh and Triplett (2006), Bick and Baker (2006), and Middeldorp (2007).

Endocrinologic Factors

Studies evaluating the relationship between various endocrinologic abnormalities have been inconsistent and have generally been

underpowered (American College of Obstetricians and Gynecologists, 2001). According to Arredondo and Noble (2006), 8 to 12 percent of recurrent miscarriages are the result of endocrine factors. Several that have been implicated are discussed.

PROGESTERONE DEFICIENCY

Insufficient progesterone secretion by the corpus luteum or placenta, also termed a *luteal phase defect* , has been suggested to cause miscarriage. Deficient progesterone production, however, may be the consequence rather than the cause of early pregnancy failure (Salem, 1984). As further discussed in Chapter 19, Serum Progesterone, the diagnostic criteria and efficacy of therapy for this proposed disorder require validation (American College of Obstetricians and Gynecologists, 2001). If the corpus luteum is removed surgically, such as for an ovarian tumor, progesterone replacement is indicated in pregnancies less than 8 to 10 weeks (Maternal Surgery).

Luteal phase defect is diagnosed when histologic dating lags behind menstrual dating by at least 2 days. The formal diagnosis also requires that two biopsies be out of phase. However, these have substantial inter- and intraobserver variability. Some have suggested that luteal phase defect can be diagnosed if the midluteal serum progesterone is less than 10 ng/mL, however, there are no studies to validate the relationship between progesterone levels and biopsy results. As many as half of women with histologically defined luteal phase defects may have normal serum progesterone levels. Furthermore, levels are frequently measured early in pregnancy, when progesterone is produced by both the corpus luteum and the trophoblast, further complicating interpretation of the results.

Treatment for presumed luteal phase defect has included progesterone supplementation, human chorionic gonadotropin administration to enhance corpus luteum function, or ovulation induction with agents such as clomiphene citrate to generate additional corpora lutea. Unfortunately, none of these treatments has been shown to be beneficial, although they are relatively benign (Reddy, 2007).

POLYCYSTIC OVARIAN SYNDROME

Women with polycystic ovaries have an increased risk for miscarriage, although the etiology remains unclear. Two main mechanisms that have been suggested are elevations in luteinizing hormone (LH) and direct effects of hyperinsulinemia on ovarian function. Both LH and β-hCG are present in the endometrium, and elevated LH concentrations may have direct deleterious effects on implantation. Another hypothesis is that chronically elevated LH levels may adversely affect oocyte development (Homburg, 1998; Watson, 1993). A third postulated mechanism is based on observations that LH induces intra-ovarian androgen levels, which are known to cause follicular atresia and poor oocyte development (Stanger, 1985; Tulppala, 1993). If we assume that elevated concentrations of LH cause miscarriage in some way, then its inhibition during a gonadotropin ovulation induction cycle might decrease miscarriage rates. In the controlled trial by Clifford (1996), however, this did not improve pregnancy outcome.

The data implicating hyperinsulinemia in pregnancy loss are somewhat stronger. Insulin modulates insulin growth factor (IGF) actions in the ovary, thereby affecting ovarian function. In one retrospective study, the miscarriage rate in women with polycystic ovarian syndrome (PCOS) was compared before and after treatment with the insulin-sensitizing medication metformin. Miscarriage rates decreased from 62 to 26 percent with treatment before and during pregnancy (Glueck, 2002). A smaller study of women with recurrent pregnancy loss was also supportive of metformin use (Jakubowicz, 2002). Taken together, these data suggest that women with PCOS who have recurrent miscarriagesâ€”and perhaps those without this historyâ€”should be treated with metformin.

DIABETES MELLITUS

Spontaneous abortion and major congenital malformation rates are both increased in women with insulin-dependent diabetes (Greene, 1999). As discussed in Diabetes Mellitus, this risk is related to the degree of metabolic control in early pregnancy. In women with recurrent miscarriage, insulin resistance has been reported to be increased (Craig, 2002). Thus, although pregnancy loss is clearly increased with poorly controlled diabetes, this risk is substantively lowered with optimal metabolic control.

HYPOTHYROIDISM

Severe iodine deficiency is associated with excessive early pregnancy loss (CastaÃ±eda, 2002). And although thyroid hormone deficiency is common in womenâ€”usually due to an autoimmune causeâ€”any effects of hypothyroidism on miscarriage have not been adequately studied. Thyroid autoantibodies are associated with an increased incidence of miscarriage, however, their role in

recurrent miscarriage is less convincing (Abramson, 2001; Esplin, 1998; Lakasing, 2005). In one investigation, Rushworth and colleagues (2000) studied 870 women with recurrent miscarriage and reported that those with antithyroid antibodies were just as likely to achieve a live birth as those without antibodies.

Because there is not a clear consensus regarding thyroid disease as a cause of recurrent miscarriage, the American College of Obstetricians and Gynecologists (2001) concludes that there is no indication for screening asymptomatic women. Conversely, overt hypothyroidism may be difficult to detect clinically, testing for it is inexpensive, and treatment is highly effective. We therefore perform thyroid-stimulating hormone (TSH) screening for women with recurrent miscarriage. We do not, however, screen for antithyroid or antimicrosomal antibodies. Although the latter provide evidence for general autoimmune dysfunction, they do not predict pregnancy loss in women with normal thyroid function (Rushworth, 2000).

Infections

As described in Infections, few infections are firmly associated with early pregnancy loss. Moreover, if any of those infections are associated with miscarriage, they are even less likely to cause recurrent miscarriage because maternal antibodies usually develop with the primary infection. Thus, there appears to be no concrete indication to screen for infection in asymptomatic women with recurrent miscarriage. Although empiric antibiotics are prescribed by some, their efficacy is unclear (Quinn, 1983a; Toth, 1986).

Evaluation and Treatment

One scheme for evaluation and treatment of women with recurrent miscarriage is outlined in Table 6-5. The timing and extent of evaluation should be based on maternal age, coexistent infertility, symptoms, and the level of anxiety. In our view, after obtaining a thorough history and examination, a modicum of testing is done. This includes parental karyotyping, uterine cavity evaluation, and testing for antiphospholipid antibody syndrome. Treatment should always be balanced between the potential morbidity and the strength of the data suggesting likely benefit.

Table 6-5 Evaluation of Couples with Recurrent Pregnancy Loss

Etiology	Diagnostic Evaluation	Abnormal	Therapy
Genetic	Karyotype partners	3â€“5%	Genetic counseling, donor gametes
Anatomic	Hysterosalpingography Hysteroscopy Sonohysterography Magnetic resonance imaging	15â€“20%	Septum transection, myomectomy, adhesiolysis, metroplasty
Endocrinologic	Midluteal progesterone	8â€“12%	Progesterone
	Thyroid-stimulating hormone		Levothyroxine
	Prolactin		Dopamine agonists
	Fasting insulin:glucose		Metformin
Immunologic	Lupus anticoagulant, antiphospholipid antibodies	15â€“20%	Heparin + aspirin
Microbiologic	Cervical cultures	5â€“10%	Antibiotics
Thrombophilia	Antithrombin III, protein C or S deficiency; factor V Leiden or prothrombin mutation	8â€“12%	Heparin + aspirin, low-molecular-weight heparin
	Hyperhomocysteinemia		Folic acid

Psychological	Interview Questionnaire	Varies	Support groups, counseling
Toxic	Tobacco, alcohol use	5%	Behavior changes
	Exposure to toxins, chemicals		Eliminate exposure

Modified from Kutteh, 2005 and Reddy, 2007, with permission.

About half of couples with recurrent miscarriage will have no explanatory findings. Nevertheless, they can be encouraged that they still may successfully achieve a live birth. The meta-analysis by Jeng and colleagues (1995) of randomized, prospective studies of couples with unexplained recurrent miscarriage determined that 60 to 70 percent had a successful subsequent pregnancy.

INDUCED ABORTION

Induced abortion is the medical or surgical termination of pregnancy before the time of fetal viability. In 2002, a total of 854,122 legal abortions were reported to the CDC (2005). These are underestimated, because clinics inconsistently report medically induced abortions. The *abortion ratio* was 246 abortions per 1,000 live births, and the *abortion rate* was 16 per 1,000 pregnant women aged 25 to 44 years. Half of these women were aged 24 years or younger, 82 percent were unmarried, and 55 percent were Caucasian. Almost 60 percent of abortions were performed during the first 8 weeks, and 88 percent during the first 12 weeks of pregnancy.

Classification of Induced Abortion

THERAPEUTIC ABORTION

Some indications for early termination of pregnancy include persistent cardiac decompensation, advanced hypertensive vascular disease, and invasive carcinoma of the cervix. In addition to medical and surgical disorders that may be indications for termination, there are others. Certainly in cases of rape or incest most consider termination indicated. Another commonly cited indication is to prevent birth of a fetus with a significant anatomic or mental deformity. The seriousness of fetal deformities is wide ranging and frequently defies social, legal, or political classification.

ELECTIVE (VOLUNTARY) ABORTION

The interruption of pregnancy before viability at the request of the woman, but not for medical reasons, is usually termed *elective* or *voluntary abortion* . These procedures comprise most abortions done today, and approximately one pregnancy is electively terminated for every four live births in the United States (Centers for Disease Control and Prevention, 2005). The Executive Board of the American College of Obstetricians and Gynecologists (2004) supports the legal right of women to obtain an abortion prior to fetal viability and considers this a medical matter between a woman and her physician.

Abortion in the United States

In 1973, the United States Supreme Court legalized abortion. Until then, only therapeutic abortions could be performed legally in most states. The most common legal definition of therapeutic abortion until then was termination of pregnancy before fetal viability for the purpose of saving the life of the mother. A few states extended their laws to read "to prevent serious or permanent bodily injury to the mother" or "to preserve the life or health of the woman". Some states allowed abortion if a pregnancy was likely to result in the birth of an infant with grave malformations.

The legality of elective abortion was established by the Supreme Court in the case of *Roe v. Wade* . The Court defined the extent to which states might regulate abortion:

1. For the stage prior to approximately the end of the first trimester, the abortion decision and the procedure must be left to the medical judgment of the attending physician.

2. For the stage subsequent to approximately the end of the first trimester, the State, in promoting its interest in the health of the mother, may, if it chooses, regulate the abortion procedures in ways that are reasonably related to maternal health.
3. For the stage subsequent to viability, the State, in promoting its interest in the potential of human life, may, if it chooses, regulate, and even proscribe abortion, except where necessary, in appropriate medical judgment, for the preservation of the life or health of the mother.

Since 1973, several other Supreme Court decisions merit citation. Borgmann and Jones (2000) have extensively reviewed these legal issues. These appellate cases originated with legislation, both state and national, that was introduced or enacted to regulate or dismantle the three provisions listed above. In general, these attempts were unsuccessful until 1989. At that time the Supreme Court ruled in the case of *Webster v. Reproductive Health Services* that states could place restrictions interfering with provision of abortion services on such items as waiting periods, specific informed consent requirements, parental/spousal notification, and hospital requirements. Based upon this decision, there are now numerous individual state restrictions that limit choice and access to abortion services. In one example, the decision to enforce parental notification in Texas in 2000 was associated with decreased abortion rates, but simultaneously increased unintended births among 17 year olds (Joyce, 2006).

Another recent choice-limiting decision is the federal law banning the poorly defined *partial birth abortion* . This law is under challenge on several fronts. The Supreme Court in mid-2007 voted 5 to 4 to uphold the Partial-Birth Abortion Act of 2003 in its review of *Gonzales v. Carhart* from Nebraska (Wright, 2006).

In its document concerning abortion policy, the American College of Obstetricians and Gynecologists (2004) states that: *The intervention of legislative bodies into medical decision making is inappropriate, ill advised, and dangerous.*

Counseling before Elective Abortion

Three choices available to a woman considering an abortion include continued pregnancy with its risks and parental responsibilities; continued pregnancy with its risks and responsibilities of arranged adoption; or the choice of abortion with its risks. Knowledgeable and compassionate counselors should objectively describe and provide information about these choices so that a woman or couple can make an informed decision.

Techniques for Early Abortion

Abortion can be performed either medically or surgically as shown in Table 6-6. Distinctive clinical features of each technique are shown in Table 6-7. Paul and colleagues (1999) summarized in detail many abortion techniques. A first-trimester pregnancy may be removed surgically by uterine curettage or by a number of medical regimens.

Table 6-6 Abortion Techniques
Surgical techniques
Cervical dilatation followed by uterine evacuation
Curettage
Vacuum aspiration (suction curettage)
Dilatation and evacuation (D&E)
Dilatation and extraction (D&X)
Menstrual aspiration
Laparotomy
Hysterotomy

Hysterectomy
Medical techniques
Intravenous oxytocin
Intra-amnionic hyperosmotic fluid
20% saline
30% urea
Prostaglandins E_2 , $F_{2?}$, E_1 , and analogues
Intra-amnionic injection
Extraovular injection
Vaginal insertion
Parenteral injection
Oral ingestion
Antiprogesterones (RU 486 [mifepristone] and epostane)
Methotrexate (intramuscular and oral)
Various combinations of the above

Table 6-7 Features of Medical and Surgical Abortion

Medical Abortion	**Surgical Abortion**
Usually avoids invasive procedure	Invasive procedure
Usually avoids anesthesia	Sedation used if desired
Requires two or more visits	Usually requires one visit
Days to weeks to complete	Complete in a predictable period
Available during early pregnancy	Available during early pregnancy
High success rate (~95%)	High success rate (99%)
Bleeding moderate to heavy for a short time	Bleeding commonly perceived as light
Requires surveillance to ensure completion of abortion	Does not require surveillance in all cases
Requires patient participation throughout a multistep process	Patient participation in a single-step process

From the American College of Obstetricians and Gynecologists, 2005b, with permission.

RESIDENCY TRAINING IN ABORTION TECHNIQUES

Because of its inherent controversial aspects, abortion training for residents in Obstetrics and Gynecology has been both championed and assailed. In some programs, such as the University of California at San Francisco, a special 6-week abortion-training elective for house staff was implemented in 1980. From 1998 through 2003, 40 residents completed training and none opted out of the rotation (Steinauer, 2005b). Other programs, such as ours at Parkland Memorial Hospital, teach residents the technical aspects of abortion by management of early missed abortions, as well as pregnancy interruption for fetal death, severe fetal anomalies, and maternal medical or surgical disorders.

Because of these differences, influenced by political and moral convictions, the American College of Obstetricians and Gynecologists (2004) respects the need and responsibility of health care providers to determine their individual positions based on personal beliefs. Certainly, physicians trained to care for women must be familiar with various abortion techniques so that complications can be managed or referrals made for suitable care (Steinauer, 2005a).

SURGICAL ABORTION

Early surgical pregnancy termination requires first dilating the cervix and then evacuating the pregnancy by mechanically scraping out the contents (sharp curettage), by suctioning out the contents (suction curettage), or both (see Sections 41-16, Sharp Dilatation and Curettage and 41-17, Suction Dilatation and Curettage). Vacuum aspiration, the most common form of suction curettage, requires a rigid cannula attached to an electric-powered vacuum source. Alternatively, manual vacuum aspiration uses a similar cannula that attaches to a handheld syringe for its vacuum source (Macisaac, 2000; Masch, 2005).

The likelihood of complications increases after the first trimester. These include uterine perforation, cervical laceration, hemorrhage, incomplete removal of the fetus and placenta, and infection. Small and large bowel injuries may also occur (Jhobta, 2007). Accordingly, sharp or suction curettage should be performed before 14 to 15 weeks.

In the absence of maternal systemic disease, abortion procedures do not require hospitalization. When abortion is performed outside a hospital setting, capabilities for cardiopulmonary resuscitation and for immediate transfer to a hospital must be available.

Hygroscopic Dilators

Trauma from mechanical dilatation can be minimized by using devices that slowly dilate the cervix. As described in Section 41-17, Suction Dilatation and Curettage, these hygroscopic dilators draw water from cervical tissues and expand, gradually dilating the cervix.

An interesting dilemma is presented by the woman who has a hygroscopic dilator placed overnight preparatory to elective abortion, but who then changes her mind. Schneider and associates (1991) described this in seven first-trimester and 14 second-trimester pregnancies. Of these, four patients returned to their original decision and underwent abortion. Of the remaining 17, there were 14 term deliveries, two preterm deliveries, and one miscarriage 2 weeks later. None suffered infectious morbidity, including three untreated women with cervical cultures positive for *Chlamydia trachomatis* . In spite of this generally reassuring report, an attitude of irrevocability with regard to dilator placement and abortion seems prudent.

Prostaglandins

Various prostaglandin preparations may be used instead of hygroscopic dilators to aid subsequent dilation. These may be taken orally or placed into the posterior vaginal fornix. In a study of self-administered misoprostol (PGE_1) at home, Oppegaard and associates (2006) reported that the oral route was unsatisfactory. Macisaac and colleagues (1999) randomized women to 400 µg of misoprostol placed vaginally 4 hours before first-trimester abortion versus laminaria placement. Misoprostol effected equal or greater dilation, caused less pain on insertion, and had fewer side effects. Timing is important, as Sharma and collaborators (2005) reported no effects with orally or vaginally administered misoprostol when given only 1 hour before early surgical abortion.

Manual Vacuum Aspiration

This office-based procedure is used for surgical treatment of early pregnancy failures as well as elective termination up to 12 weeks' gestation. Masch and Roman (2005) recommend that pregnancy terminations in the office with this method be limited to 10 weeks or less. Certainly, blood loss rises sharply between 10 and 12 weeks (Westfall, 1998).

The procedure uses a hand-operated 60-mL syringe and cannula. A vacuum is created in the syringe and attached to the cannula, which is inserted transcervically into the uterus. The vacuum is created and produces up to 60 mm Hg suction. Although complications are similar to other surgical methods, they are not increased (Goldberg, 2004).

With pregnancies less than 8 weeks, no cervical preparation is required. After this time, some recommend either osmotic dilators placed the day before or misoprostol given 2 to 4 hours before the procedure. A paracervical block with or without intravenous sedation, or conscious sedation is used for anesthesia (see Chap. 40, Usage).

Menstrual Aspiration

Aspiration of the endometrial cavity within 1 to 3 weeks after a missed menstrual period using a flexible 5- or 6-mm Karman cannula (see Fig. 41-17.3) and attached syringe has been referred to as *menstrual extraction, menstrual induction, instant period, traumatic abortion,* and *mini-abortion* . At this early gestation, pregnancy can be misdiagnosed, an implanted zygote can be missed by the curette, ectopic pregnancy can be unrecognized, or infrequently, the uterus is perforated. Even so, Paul and associates (2002) reported a 98-percent success rate in more than 1,000 women who underwent this procedure. A positive pregnancy test result will eliminate a needless procedure on a nonpregnant woman whose period has been delayed for other reasons.

To identify placenta in the aspirate, Macisaac and Darney (2000) recommend that the syringe contents are rinsed in a strainer to remove blood. They are then placed in a clear plastic container with saline and examined with back lighting. Placental tissue macroscopically appears soft, fluffy, and feathery. A magnifying lens, colposcope, or microscope can also improve visualization.

Laparotomy

In a few circumstances, abdominal hysterotomy or hysterectomy for abortion is preferable to either curettage or medical induction. If significant concurrent uterine disease is present, hysterectomy may provide ideal treatment. Either hysterotomy with tubal ligation or, on occasion, hysterectomy may be indicated for women who desire pregnancy termination and sterilization. At times, a failed medical induction during the second trimester may necessitate hysterotomy or hysterectomy.

MEDICAL ABORTION

Throughout history, many naturally occurring substances have been tried as abortifacients. Most often, serious systemic illness or even death has resulted rather than abortion. Even today, only a few effective, safe abortifacient drugs are used.

According to the American College of Obstetricians and Gynecologists (2005b), outpatient medical abortion is an acceptable alternative to surgical abortion in appropriately selected women with pregnancies less than 49 days of gestation. Beyond this point, the available data, though less robust, support surgical abortion as a preferable method of early abortion.

Three medications for early medical abortion have been widely studied and used: the antiprogestin *mifepristone* ; the antimetabolite *methotrexate* ; and the prostaglandin *misoprostol* . These agents cause abortion by increasing uterine contractility either by reversing the progesterone-induced inhibition of contractions (mifepristone and methotrexate), or by stimulating the myometrium directly (misoprostol). In addition, mifepristone causes cervical collagen degradation, possibly because of increased expression of matrix metalloproteinase-2 (Clark, 2006).

A variety of dosing schemes have proven effective (Table 6-8). Mifepristone or methotrexate is administered initially, and followed after some time interval by misoprostol. Alternatively, at least for "pregnancy failures", (i.e., anembryonic gestation, embryonic or fetal death, and incomplete or inevitable abortion), 800 µg misoprostol given vaginally as a sole agent was effective in causing complete expulsion by day 8 in 84 percent of women treated (Zhang, 2005). Methotrexate and misoprostol are teratogens, and their use thus requires a commitment on the part of both a woman and her caregiver to complete the abortion.

Table 6-8 Regimens for Medical Termination of Early Pregnancy

Mifepristone/misoprostol
[a] Mifepristone, 100â€“600 mg orally followed by:
[b] Misoprostol, 200â€“600 µg orally or 800 µg vaginally in 6â€“72 hours
Methotrexate/misoprostol
[c] Methotrexate, 50 mg/m^2 intramuscularly or orally followed by:
[d] Misoprostol, 800 µg vaginally in 3â€“7 days; repeat if needed 1 week after methotrexate initially given
Misoprostol alone
800 µg vaginally, repeated for up to three doses

[a] Doses of 200 and 600 µg are similarly effective.

[b] Oral route may be less effective, possibly more side effects (nausea and diarrhea). May also be given sub- lingually, but with more side effects.

[c] Efficacy similar for both routes of administration.

[d] Similar efficacy when given on day 3 versus day 5.

Data from the American College of Obstetricians and Gynecologists, 2005b; Borgatta, 2001; Bracken, 2007; Creinin, 2001, 2007; Hamoda, 2005; Jain, 2002; Kulier, 2004; Pymar, 2001; Schaff, 2000; Shannon, 2006; von Hertzen, 2003, 2007; Wiebe, 1999, 2002

Contraindications to medical abortion have evolved from the exclusion criteria of various clinical trials. In addition to specific allergies to the medicines, they have included an in situ intrauterine device, severe anemia, coagulopathy or anticoagulant use, and significant medical conditions such as active liver disease, cardiovascular disease, and uncontrolled seizure disorders. Additionally, because misoprostol can lower glucocorticoid activity, women with adrenal disease or with disorders requiring glucocorticoid therapy should be excluded (American College of Obstetricians and Gynecologists, 2005b). A modified methotrexate dose should be given with cautionâ€”if at allâ€”in women with renal insufficiency (Kelly, 2006). Women contemplating medical abortion should receive thorough counseling regarding the risks, benefits, and requirements of both medical and surgical approaches.

With the mifepristone regimen, according to the U.S. Food and Drug Administration (FDA) package labeling, misoprostol is to be provider-administered. Afterwards, the woman typically remains in the office for 4 hours, although her activity is not restricted. If the pregnancy appears to have been expelled, she is examined to confirm expulsion. If during observation the pregnancy does not appear to have been expelled, a pelvic examination is performed prior to discharge, and the woman re-appointed for 1 to 2 weeks. At this later appointment, if clinical examination or sonographic evaluation fails to confirm completed abortion, a suction procedure usually is done.

In regimens employing methotrexate, women are typically seen at least 24 hours after misoprostol, and approximately 7 days after methotrexate administration, at which time a sonographic examination is performed. If the pregnancy persists, another dose of misoprostol is given, and the woman is seen again in 1 week if fetal cardiac activity is present, or in 4 weeks if there is no fetal cardiac activity. If by the second visit, abortion has not occurred, it is usually completed by suction curettage.

Bleeding and cramping with medical termination can be significantly worse than symptoms experienced with menses. Adequate pain medication, usually including a narcotic, should be provided. According to the American College of Obstetricians and Gynecologists (2005b), soaking two pads or more per hour for at least 2 hours is a threshold at which a woman should be instructed to contact her provider, who can determine whether she needs to be seen.

Early medical abortion is highly effectiveâ€”90 to 98 percent of women will not require surgical intervention (Kahn, 2000). According to Hausknecht (2003), there were only 139 complications reported to the manufacturer with mifepristone when given with misoprostol to 80,000 women for medical abortion.

Unnecessary surgical intervention in women undergoing medical abortion can be avoided if sonographic results are interpreted appropriately. Specifically, if no gestational sac is present, in the absence of heavy bleeding, intervention in most women is unnecessary. This is true even when, as is common, the uterus contains sonographically evident debris.

Consequences of Elective Abortion

MATERNAL MORTALITY

Legally induced abortion, performed by trained gynecologists, especially when performed during the first 2 months of pregnancy, has a mortality rate of less than 1 per 100,000 procedures (Grimes, 2006). Early abortions are safer, and the relative risk of dying as the consequence of abortion approximately doubles for each 2 weeks after 8 weeks' gestation. According to Horon (2005), these deaths are underreported.

IMPACT ON FUTURE PREGNANCIES

In a scholarly review of the impact of elective abortion on subsequent pregnancy outcome, Hogue (1986) summarized data from more than 200 publications. Data relating abortion to subsequent pregnancy outcome are observational, and therefore subject to bias and uncontrolled confounding factors. All studies on this topic must be interpreted with these limitations in mind. That said, fertility does not appear to be diminished by an elective abortion, except infrequently as a consequence of infection. Most studies indicate that vacuum aspiration does not increase the subsequent incidence of second-trimester spontaneous abortion or preterm delivery. The case-control French EPIPAGE (epidemiologic des Petits Ages Gestationnels) study, however, found a 1.5-fold increased incidence of very preterm deliveryâ€”22 to 32 weeksâ€”in women with a history of induced abortion (Moreau, 2005). Subsequent ectopic pregnancies are not increased after elective abortion, except possibly in women with preexisting chlamydial infection or in those who develop postabortion infections. Multiple sharp curettage abortion procedures may increase the subsequent risk of placenta previa, whereas vacuum aspiration procedures likely do not (Johnson, 2003).

The recent study by Virk and colleagues (2007) of 11,814 Danish women undergoing first-trimester elective abortions is informative to compare outcomes with types of abortion. They compared subsequent pregnancy outcomes in 2,710 women undergoing medically induced termination with 9,104 who had a surgical abortion. There were no significant differences between the two groups for ectopic pregnancyâ€"about 2.5 percent, miscarriageâ€"about 6 percent, and subsequent low birthweight neonatesâ€"about 4.5 percent.

RESUMPTION OF OVULATION FOLLOWING MISCARRIAGE

Ovulation may resume as early as 2 weeks after an early pregnancy is terminated, whether spontaneously or induced. Lahteenmaki and Luukkainen (1978) detected surges of LH at 16 to 22 days after abortion in 15 of 18 women studied. Plasma progesterone levels, which had plummeted after the abortion, increased soon after LH surges. These hormonal events agree with histologic changes observed in endometrial biopsies (Boyd, 1972). **Therefore, if pregnancy is to be prevented, effective contraception should be initiated soon after abortion** .

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ECTOPIC PREGNANCY: INTRODUCTION

An ectopic or extrauterine pregnancy is one in which the blastocyst implants anywhere other than the endometrial lining of the uterine cavity. In some form, they account for 1.3 to 2 percent of reported pregnancies in the United States (Zane, 2002). With the advent of a sensitive and specific radioimmunoassay for the β-subunit of human chorionic gonadotropin (β-hCG), combined with high-resolution transvaginal sonography (TVS), the initial presentation of a woman with an ectopic pregnancy is seldom life-threatening as it was in the past. Nevertheless, ectopic pregnancies remain an important cause of morbidity and mortality in the United States with an estimated total cost of nearly $295 million in 1998 (Rein, 2000).

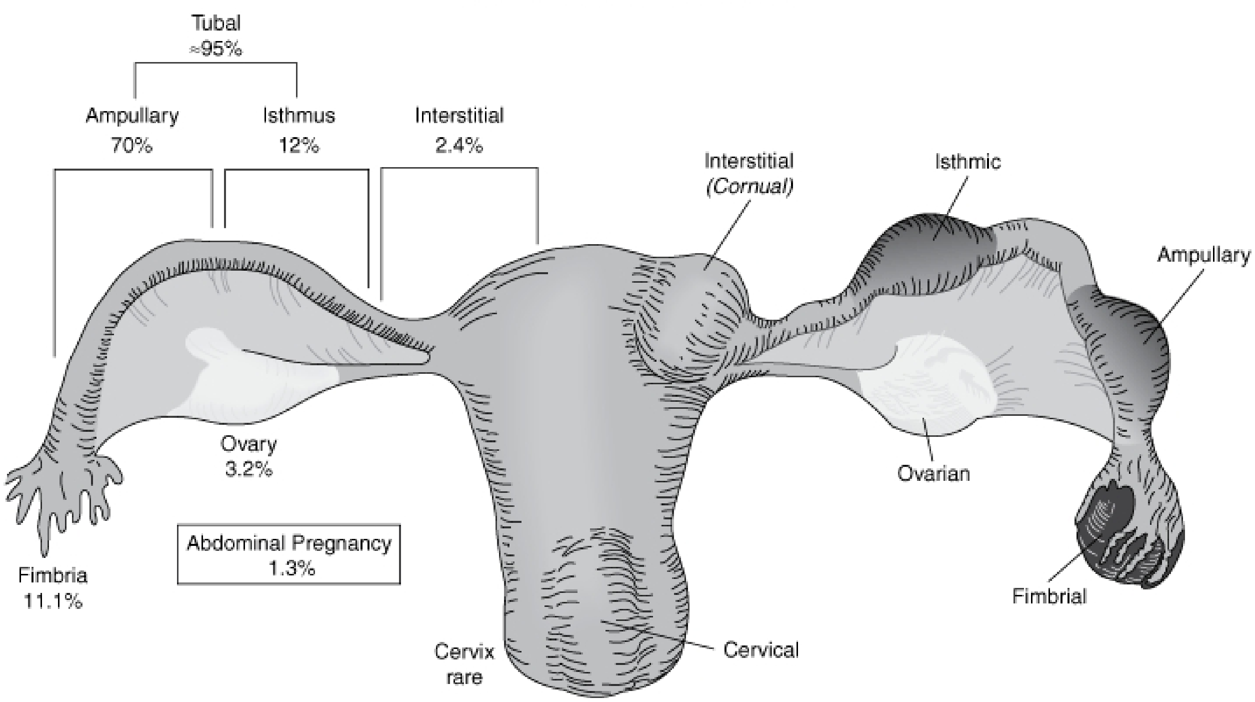
GENERAL CONSIDERATIONS

Classification

Nearly 95 percent of ectopic pregnancies implant in the fallopian tube. Shown in Fig. 7-1 are implantation sites for 1,800 surgically treated ectopic pregnancies. Almost 95 percent were tubal pregnancies, 3.2 percent ovarian, and 1.3 percent were abdominal (Bouyer, 2002). Bilateral ectopic pregnancies are rare and their estimated prevalence is 1 of every 200,000 pregnancies (al-Awwad, 1999).

FIGURE 7-1

SITES OF ECTOPIC PREGNANCY



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Various sites and frequency of ectopic pregnancies. *(Modified from Callen, 2000, with permission.)*

Epidemiology

Reported ectopic pregnancy incidence rates are not as reliable as in the past. The dramatic improvements in diagnosis and outpatient treatment protocols render hospital statistics invalid. According to the Centers for Disease Control and Prevention (1995), the rate of ectopic pregnancy has increased in the United States nearly fourfold, from 4.5 per 1,000 pregnancies in 1970 to 19.7 per 1,000 pregnancies in 1992. This rate is similar to recent estimates by Kaiser Permanente of North California of 20.7 per 1,000 pregnancies from 1997 to 2000 (Van Den Eeden, 2005).

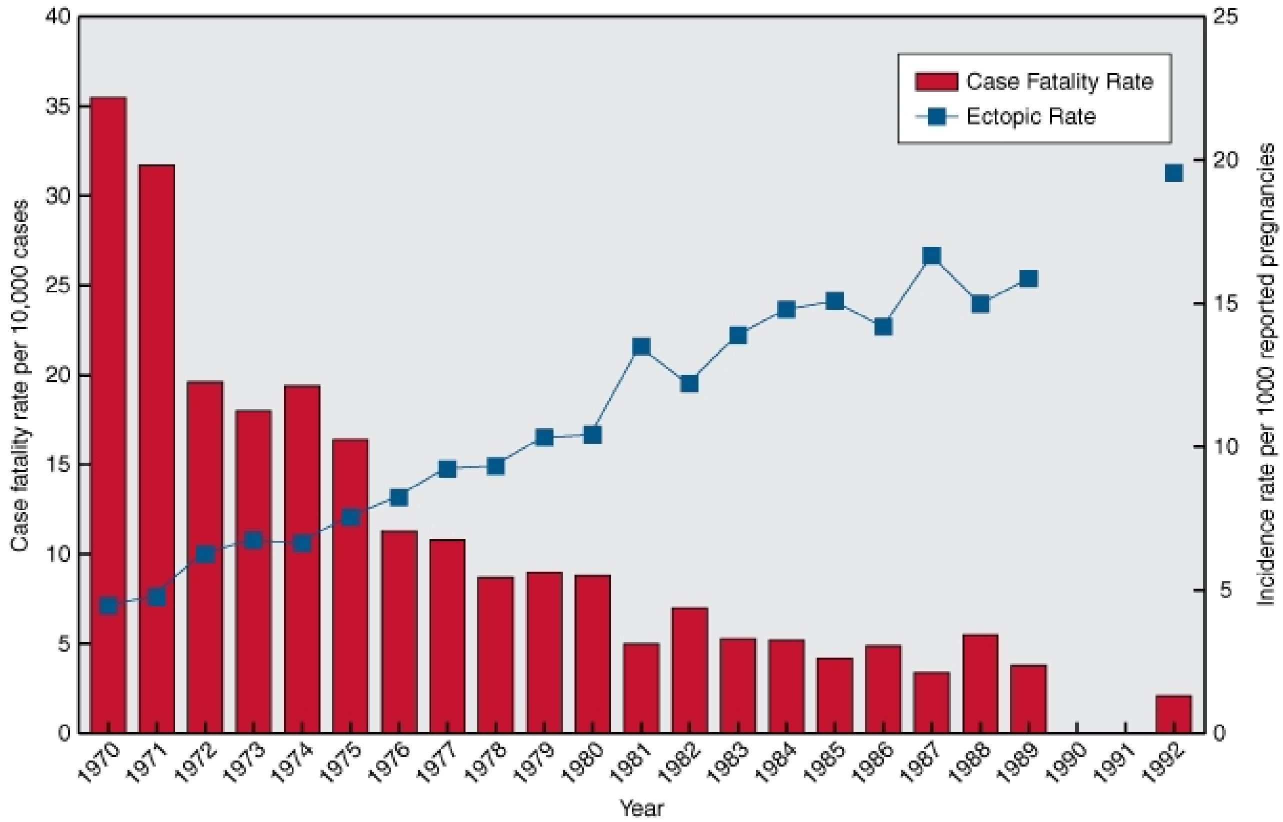
A number of factors help to explain the increased incidence of ectopic pregnancies:

1. There is a greater prevalence of sexually transmitted diseases, specifically chlamydial infections (Rajkhowa, 2000).
2. Identification has improved through the use of more sensitive diagnostic tools.
3. Tubal factor infertility, including restoration of tubal patency or documented tubal pathology has increased (Ankum, 1996).
4. Delayed childbearing is more prevalent and has been accompanied by an increased use of assisted reproductive technologies, which carry increased risk of ectopic pregnancy.
5. Intrauterine device (IUD) and tubal sterilization rates have increased and failures predispose to ectopic pregnancy (Mol, 1995).

Mortality

Ectopic pregnancy remains the leading cause of early pregnancy-related death. Still, current diagnostic and treatment protocols have resulted in a 10-fold decline in the case fatality rate over the past 35 years. The rate in 1970 was 35.5 deaths per 10,000 ectopic pregnancies compared with 3.8 per 10,000 in 1989. This was despite the fivefold increase in ectopic pregnancy from 17,800 in 1970 to 108,000 in 1992 (Fig. 7-2). Racial disparities affect ectopic pregnancy-related deaths. A nonwhite woman had an overall risk of death 3.4 times higher than a white woman for the 20-year period from 1970 to 1989 (Goldner, 1993). This was true for all age groups as shown in Fig. 7-3. Inadequate access to gynecologic and prenatal care may partially explain this trend.

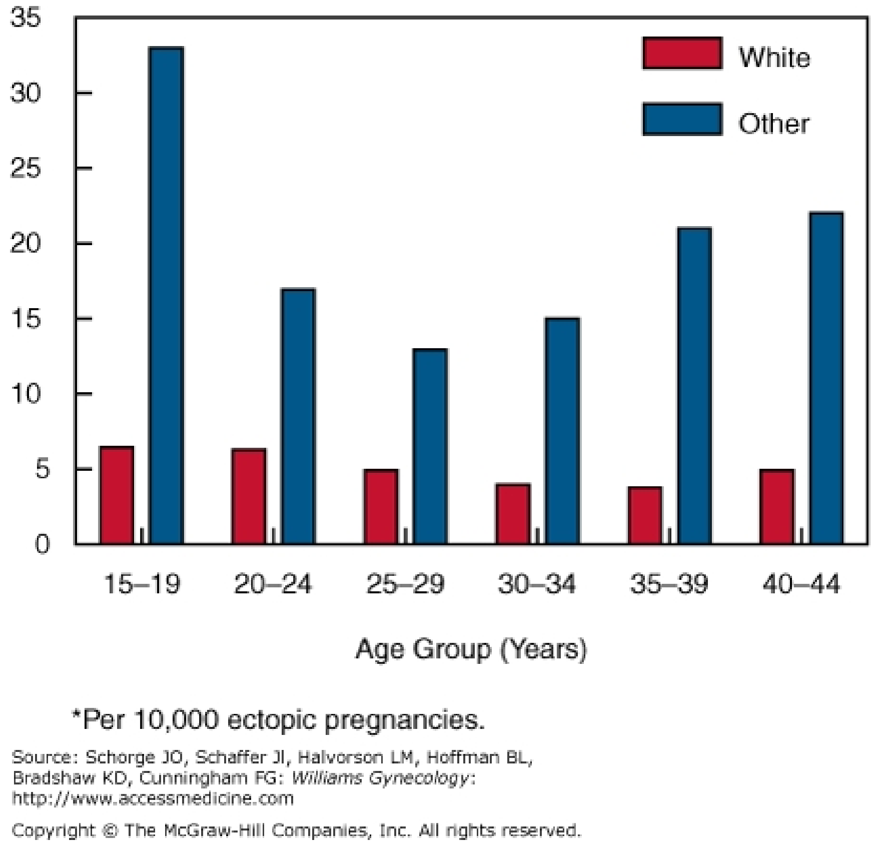
FIGURE 7-2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Case fatality rate and incidence of ectopic pregnancy. *(Data from Centers for Disease Control and Prevention, 1995, with permission).*

FIGURE 7-3



Case fatality rates for ectopic pregnancy by race and age in the United States, 1970 to 1989. *(From Goldner, 1993, with permission.)*

TUBAL RUPTURE

Rupture can lead to severe hemorrhage with resulting morbidity and mortality. Over the past two decades, the rate of rupture with ectopic pregnancy ranged from 20 to 35 percent (Job-Spira, 1999; Saxon, 1997). Three risk factors that increase the likelihood of tubal rupture include ovulation induction, serum β-hCG level exceeding 10,000 IU/L when ectopic pregnancy is first suspected, and a history of never having used contraception. Appreciation of these risk factors aids a timely diagnosis and prompt surgical intervention. Importantly, minimally invasive treatment options are limited if hemodynamic instability follows tubal rupture.

There may be a difference between an "acute" and a "chronic" ectopic pregnancy with regard to the risk of tubal rupture. Acute ectopic pregnancies are those with a high serum β-hCG level at presentation and rapid growth. These carry the highest risk of tubal rupture compared with chronic ectopic pregnancies, which demonstrate static serum β-hCG levels (Barnart, 2003c). Theoretically, an acute ectopic pregnancy has healthy growing trophoblastic cells that do not result in early bleeding, and women thus present for care later. This is compared with the chronic form, which has abnormal trophoblastic cells, which die early, have lower serum β-hCG levels, and present with early pregnancy bleeding that leads to earlier diagnosis.

Timing of tubal rupture is partially dependent on pregnancy location. As a rule, tubes rupture earlier if implantation is in the isthmic or ampullary portion. Later rupture is seen if the ovum implants within the interstitial portion. Rupture is usually spontaneous, but can also be caused by trauma such as that associated with bimanual pelvic examination or coitus.

Tubal Damage

Ultimately, there does not seem to be a direct correlation between tubal damage following ectopic pregnancy and long-term prognosis for subsequent pregnancy. Job-Spira and colleagues (1999) reported that rupture does not have an independent effect on the 1-year cumulative frequency of subsequent uterine pregnancy.

Elito and colleagues (2005) prospectively evaluated tubal patency using hysterosalpingography after conservative therapy for

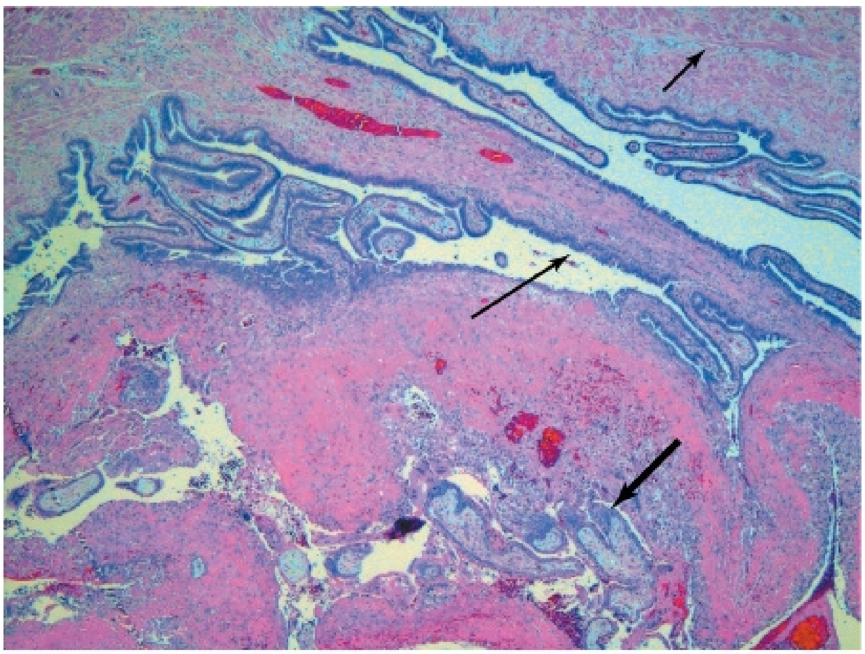
ectopic pregnanciesâ€"either expectant management or systemic methotrexate. They found an initial serum β-hCG level >5000 IU/L carried a 12-fold increased risk of subsequent tubal obstruction. However, there was no relationship with obstruction and ectopic size, or sonographic landmarks such as a tubal ring seen using color flow Doppler.

PATHOPHYSIOLOGY

Histopathology

Lack of a submucosal layer within the fallopian tube wall provides easy access for the fertilized ovum to burrow through the epithelium and allow implantation within the muscular wall. As the rapidly proliferating trophoblast erodes the subjacent muscularis layer, maternal blood pours into the spaces within the trophoblast or the adjacent tissue. The lack of resistance allows early penetration by trophoblasts as shown in Fig. 7-4. The anatomic location of a tubal pregnancy may predict the extent of damage. Senterman and colleagues (1988) studied histologic samples from 84 isthmic and ampullary pregnancies and reported that half of the ampullary pregnancies were intraluminal and the muscularis was preserved in 85 percent of these. Conversely, isthmic gestations were found both intra- and extraluminally with more disruption of the tubal wall.

FIGURE 7-4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photomicrograph of early tubal rupture. Chorionic villi (**thick arrow**) can be seen within the tubal lumen. The **long black** arrow identifies the tubal epithelium and the **short black arrow** marks the tubal muscularis layer. *(Courtesy Dr. Raheela Ashfaq.)*

Inflammation

Acute inflammation has been implicated in the role of tubal damage that predisposes to ectopic pregnancies. Chronic salpingitis and salpingitis isthmica nodosa also have important roles in ectopic pregnancy development (Kutluay, 1994).

Recurrent chlamydial infection causes intraluminal inflammation and subsequent fibrin deposition with tubal scarring (Hillis, 1997). Whereas endotoxin-producing *Neisseria gonorrhoeae* causes virulent pelvic inflammation that has a rapid clinical onset, the chlamydial inflammatory response is chronic and peaks at 7 to 14 days. Persistent chlamydial antigens can trigger a delayed hypersensitivity reaction with continued scarring despite negative cultures (Toth, 2000).

Prior conservative, pharmacologically-induced abortionâ€"but not surgical terminationâ€"is associated with an increased risk for

ectopic pregnancy (Bouyer, 2003; Tharaux-Deneux, 1998). Antibiotic prophylaxis at the time of suction curettage abortion may have a protective effect from infection-related inflammatory tubal damage. For example, in a study by Sawaya and colleagues (1996), peri-procedural antibiotics decreased the risk of upper genital tract infection by 42 percent.

RISK FACTORS

An appreciation of risk factors for ectopic pregnancy leads to a more timely diagnosis with improved maternal survival and future reproductive potential. As summarized in Table 7-1, a prior ectopic pregnancy, documented tubal pathology, surgery to restore tubal patency, or tubal sterilization carry the highest risks of obstruction and subsequent ectopic pregnancy. A woman with two prior ectopic pregnancies has a 10-fold chance for another (Skjeldestad, 1998).

Table 7-1 Risk Factors for Ectopic Pregnancy

Factor	Odds Ratio (95% CI)
Prior ectopic pregnancy	12.5 (7.5, 20.9)
Prior tubal surgery	4.0 (2.6, 6.1)
Smoking >20 cigarettes per day	3.5 (1.4, 8.6)
Prior STD with confirmed PID by laparoscopy and/or positive test for *Chlamydia trachomatis*	3.4 (2.4, 5.0)
Three or more prior spontaneous miscarriages	3.0 (1.3, 6.9)
Age ≥40 years	2.9 (1.4, 6.1)
Prior medical or surgical abortion	2.8 (1.1, 7.2)
Infertility >1 year	2.6 (1.6, 4.2)
Lifelong sexual partners >5	1.6 (1.2, 2.1)
Previous IUD use	1.3 (1.0, 1.8)

IUD = intrauterine device; PID = pelvic inflammatory disease; STD = sexually transmitted disease.

Data from Bouyer, 2003 and Buster, 1999, with permission.

Smoking, which may be a surrogate marker for sexually transmitted infections, increases the risk of ectopic pregnancy three- to fourfold in women who smoke more than one pack of cigarettes daily (Saraiya, 1998).

The use of assisted reproductive technology for sub- or infertile couples has a 0.8-percent incidence of ectopic pregnancy per transfer and 2.2 percent per clinical pregnancy (Coste, 2000). Procedures leading to the highest rates are gamete intrafallopian transfer (GIFT) (3.7 percent), cryopreserved embryo transfer (3.2 percent), and in vitro fertilization (IVF) (2.2 percent) (American Society for Reproductive Medicine and Society for Assisted Reproductive Technology, 2002). In women undergoing IVF, the main risk factors for ectopic pregnancy are tubal factor infertility and hydrosalpinges (Strandell, 1999; Van Voorhis, 2006). Moreover, "atypical" implantationâ€"cornual, abdominal, cervical, ovarian, or heterotopicâ€"is more common following assisted reproductive procedures.

Women aged 35 to 44 years have a threefold risk of ectopic pregnancy compared with those aged 15 to 25 years (Goldner, 1993). These have been attributed to age-related hormonal changes that alter tubal function (Coste, 2000).

Most forms of contraception will ironically increase the relative incidence of ectopic pregnancy by decreasing the number of intrauterine pregnancies. The relative number of ectopic pregnancies varies by contraceptive use. For example, barrier contraception and the TCu380A IUD do not confer an increased ectopic pregnancy rate (van Os, 1999). Most other forms do, and

the levonorgestrel-containing intrauterine system (Mirena, Berlex, Montville, NJ) has a 5-year cumulative pregnancy rate of 0.5 per 100 users of which half are ectopic (Backman, 2004). Progesterone-only contraceptive pills have a slightly increased rate because of their effects to diminish tubal motility. Tubal sterilization can be followed by an ectopic pregnancy. This risk is doubled in women younger than 30 years at the time of sterilization, partially because of age-related fecundity. Bipolar cautery has failure rates of 3.2 per 1000 procedures, compared with puerperal partial salpingectomy, which has a rate of 1.2 per 1000 procedures (Peterson, 1997).

CLINICAL MANIFESTATIONS

Symptoms

As women seek care earlier, the ability to diagnose ectopic pregnancy before ruptureâ€"even before the onset of symptomsâ€"is not unusual. Despite the classic symptoms of amenorrhea followed by vaginal bleeding and/or abdominal pain on the affected side, there is no constellation of symptoms that secure the diagnosis with reliability (Dart, 1999). Other pregnancy discomforts such as breast tenderness, nausea, and urinary frequency may accompany more ominous findings. These include shoulder pain worsened by inspiration, which is caused by phrenic nerve irritation from subdiaphragmatic blood, or vasomotor disturbances such as vertigo and syncope from hemorrhagic hypovolemia.

Many women with a small unruptured ectopic pregnancy have unremarkable clinical findings. Nevertheless, the diagnosis should be considered strongly when any of the above symptoms are reported by reproductive-aged women, especially those with risk factors for an extrauterine pregnancy.

Clinical Findings

VITAL SIGNS

Although some women have orthostatic findings, normal vital signs are unreliable to exclude a ruptured ectopic pregnancy. Birkhahn and associates (2003) employed the Shock Index to evaluate the possibility of ruptured ectopic pregnancy. This index reflects heart rate divided by systolic blood pressure and is used to evaluate trauma patients for hypovolemic or septic shock upon presentation. The normal range lies between 0.5 and 0.7 for nonpregnant patients. These investigators reported that a Shock Index of >0.85 increased by 15-fold the likelihood of a ruptured ectopic pregnancy.

Abdominal and pelvic findings are notoriously scant in many women before tubal rupture. With rupture, however, nearly three-fourths will have marked tenderness on both abdominal and pelvic examination and have pain that is aggravated with cervical manipulation. A pelvic mass, including fullness posterolateral to the uterus, can be palpated in about 20 percent of women. Initially, the ectopic pregnancy may feel soft and elastic, whereas extensive hemorrhage produces a firmer consistency. Many times discomfort precludes palpation of the mass, and limiting examinations may help avert iatrogenic rupture.

DIFFERENTIAL DIAGNOSIS

Symptoms of ectopic pregnancy can mimic multiple entities (Table 7-2). Early pregnancy complications such as threatened, incomplete, or missed abortion; placental polyp; or hemorrhagic corpus luteal cyst may be difficult to differentiate without histologic diagnosis (Barnhart, 2003b). Moreover, early bleeding occurs in about 20 percent of women with normal pregnancies.

Table 7-2 Conditions that Cause Lower Abdominal Pain

Cause	Location	Characteristics	Associated Findings
Pregnancy			
Abortion	Midline or generalized	Crampy, intermittent	(+) UCG; vaginal bleeding
Ectopic	Unilateral or generalized	Crampy, continuous	(+) UCG; vaginal bleeding
Uterus and Cervix			
Cervicitis	Lower abdominal pain	Dull, aching	Vaginal discharge, possible low-grade fever
Endometriosis	Midline	Variable; worse with certain activities	Adnexal mass if endometrioma present
Degenerating leiomyoma	Variable	Dull, sharp, aching	Irregular, enlarged uterus
Adnexal Disease			
Salpingitis	Diffuse	Severe	Moderate to high fever
Tubo-ovarian abscess	Unilateral	Intermittent	Usually high fever
Adnexal torsion	Lower quadrant	Acute, crampy, sudden onset	
Corpus luteum cyst	Unilateral	Sudden onset	(+/â€“) UCG
Other			
Appendicitis	Periumbilical, right lower quadrant		Anorexia, nausea, vomiting
Mesenteric lymphadenitis	Right lower quadrant		
Cystitis	Midline, suprapubic	Acute, spasms	Dysuria, frequency
Renal calculi	Flank, radiating to lower abdomen	Severe, intermittent	Hematuria

UCG = urinary chorionic gonadotropin.

A number of nonpregnancy-related disorders can mimic ectopic pregnancy (see Table 7-2). In general, a positive test for β-hCG usually excludes these other diagnoses, but the presence of a concurrent pregnancyâ€”either uterine or ectopicâ€”is always possible.

DIAGNOSIS

Serial serum β-hCG measurements and TVS are the most valuable diagnostic aids to confirm the clinical suspicions of an ectopic pregnancy.

Laboratory Findings

SERUM β-HCG MEASUREMENTS

Chorionic gonadotropin can be detected in serum as early as 8 days after the luteinizing hormone (LH) surge. In normal pregnancies, serum β-hCG levels rise in a log-linear fashion until 60 or 80 days after the last menses, at which time values plateau at about 100,000 IU/L. Given an interassay variability of 5 to 10 percent, interpretation of serial values is more reliable when performed by the same laboratory. With a robust uterine pregnancy, serum β-hCG levels should increase between 53 and 66 percent every 48 hours (Barnhart, 2004a; Kadar, 1982). Inappropriately rising serum β-hCG levels only indicate a dying pregnancy, not its location.

Many women present with an unsure last menstrual period, and an educated guess of gestational age is made. In these cases, correlation between the serum β-hCG concentration and TVS findings becomes especially important.

SERUM PROGESTERONE

Determination of serum progesterone concentration is used by some to diagnose ectopic pregnancy when serum β-hCG determinations and sonographic findings are inconclusive (Carson, 1993; Stovall, 1992). There is minimal variation in serum progesterone concentration between 5 and 10 weeks' gestation, thus a single value is sufficient. Mol and colleagues (1998) performed a meta-analysis of 22 studies to assess the accuracy of a single serum progesterone level to differentiate ectopic from uterine pregnancy. They found that results were most accurate when approached from the viewpoint of *healthy versus dying pregnancy* . With serum progesterone levels of <5 ng/mL, a dying pregnancy was detected with near perfect specificity and with a sensitivity of 60 percent. Conversely, values of >20 ng/mL had a sensitivity of 95 percent with specificity around 40 percent to identify a healthy pregnancy. Ultimately, serum progesterone can only be used to buttress a clinical impression, but cannot differentiate between an ectopic and uterine pregnancy.

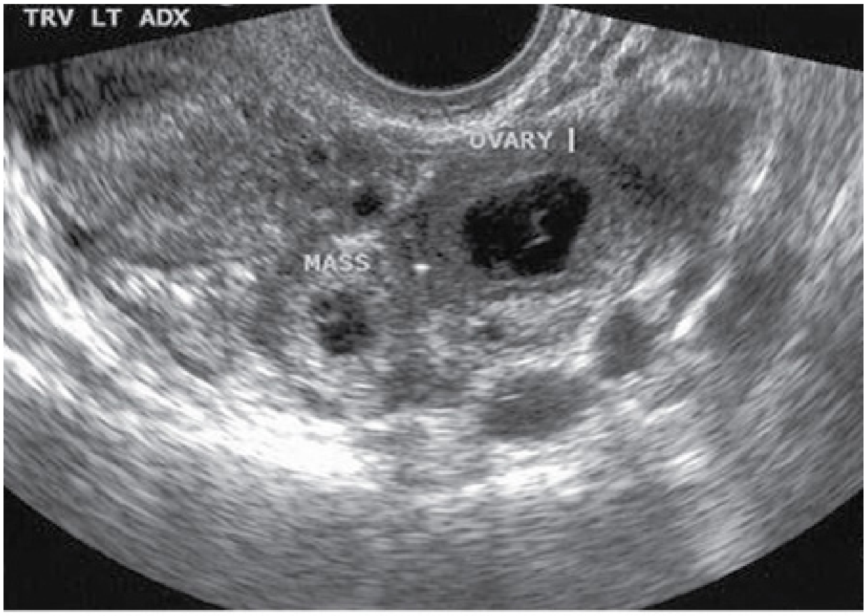
HEMOGRAM

After sufficient hemorrhage, restoration of normal blood volume takes place during the following 12 to 24 hours. Resulting hemodilution causes a decrease in hemoglobin concentration or hematocrit level during this time and their serial determinations are valuable markers of hemorrhage severity. Marked leukocytosis, especially if accompanied by fever, suggests an infection-related disorder.

Sonography

High-resolution sonography has revolutionized the clinical management of a woman with a suspected ectopic pregnancy. Using TVS, a gestational sac is usually visible between 4.5 and 5 weeks, the yolk sac appears between 5 and 6 weeks, and a fetal pole with cardiac activity is first detected at 5.5 to 6 weeks (Fig. 7-5). With transabdominal sonography these structures are visualized slightly later.

FIGURE 7-5



Transvaginal sonography of ectopic pregnancy. Note the adnexal mass distinct from the ovary and also the yolk sac seen within the gestational sac. *(Courtesy of Dr. Elysia Moschos.)*

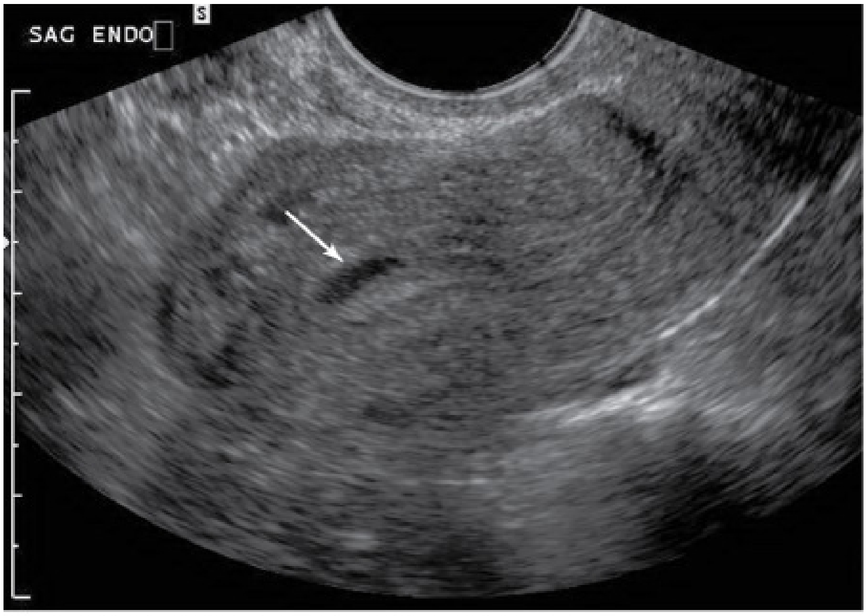
When the last menstrual period is unknown, serum β-hCG testing is used to define expected sonographic findings. Each institution must define a β-hCG discriminatory value, that is, the lower limit at which an examiner can reliably visualize pregnancy. At most institutions, a concentration between 1,500 and 2,000 IU/L represents this value.

Accurate diagnosis by sonography is three times more likely if the initial β-hCG level is above this value. The absence of uterine pregnancy with β-hCG levels above the discriminatory value signifies an abnormal pregnancyâ€"either ectopic, incomplete abortion, or resolving completed abortion. Conversely, sonographic findings obtained when β-hCG values lie below the discriminatory value are not diagnostic in nearly two-thirds of cases (Barnhart, 1999). Moreover, routine sonography without a clinical suspicion of ectopic pregnancy does not improve diagnostic and triage efficiency.

Systematic sonographic evaluation is critical to establish the correct diagnosis. Most begin with the endometrial cavity. In pregnancies conceived spontaneously, identification of a uterine pregnancy effectively excludes the possibility of an ectopic implantation. When assisted reproductive technologies are employed, however, careful examination of the tube and ovary is performed even with a uterine pregnancy because heterotopic pregnancy rates may be as high as 1 per 100 (Tal, 1996).

An intracavitary fluid collection caused by sloughing of the decidua can create a *pseudogestational sac* , or *pseudosac* . As shown in Fig. 7-6, this one-layer sac is typically situated in the midline of the uterine cavity, whereas a normal gestational sac is eccentrically located (Dashefsky, 1988). A trilaminar endometrial pattern is unique for the diagnosis of ectopic pregnancy; its specificity is 94 percent, but its sensitivity is only 38 percent (Hammoud, 2005).

FIGURE 7-6



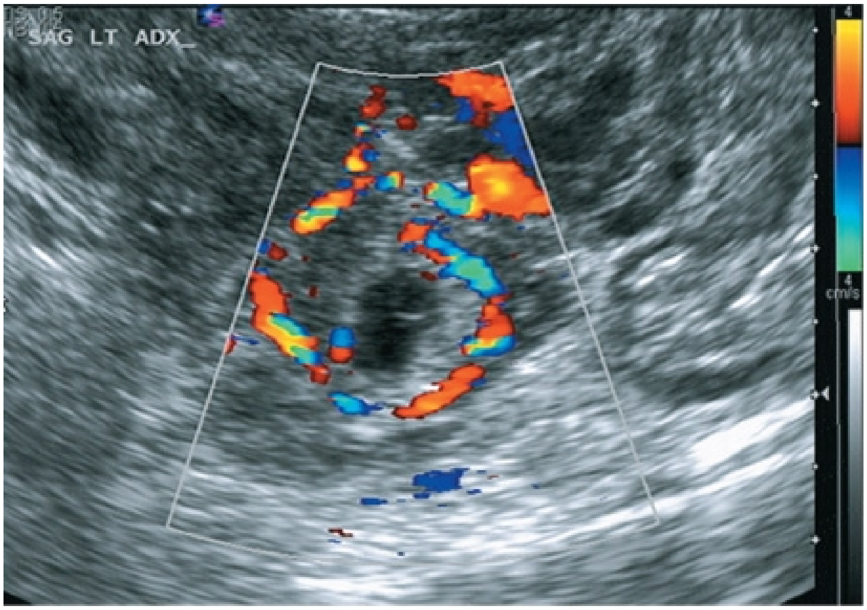
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Transvaginal sonography of a pseudogestational sac within the endometrial cavity (arrow). Note its ovoid shape and central location, which are characteristic of these fluid collections. *(Courtesy of Dr. Elysia Moschos.)*

The fallopian tubes and ovaries are also inspected. Visualization of an extrauterine yolk sac or embryo clearly confirms a tubal pregnancy, although such findings are present in only 15 to 30 percent of cases (Paul, 2000). In some cases, a halo or tubal ring surrounded by a thin hypoechoic area caused by subserosal edema can be seen. According to Burry and associates (1993), this has a positive predictive value of 92 percent and a sensitivity of 95 percent. Brown and associates (1994) conducted a meta-analysis of 10 studies to ascertain the best transvaginal sonographic criteria to diagnose ectopic pregnancy. They reported that the finding of any adnexal mass, other than a simple ovarian cyst, was the most accurate, with a sensitivity of 84 percent, specificity of 99 percent, positive predictive value of 96 percent, and negative predictive value of 95 percent.

Differentiation of an ectopic pregnancy from a corpus luteal cyst can be challenging (see Chap. 9, Diagnosis and Treatment). Swire and co-workers (2004) observed that the wall of the corpus luteum is less echogenic compared with both the *halo* and the endometrium. They found that a sponge-like, lace-like, or reticular pattern seen within the cyst is classic for hemorrhage (see Fig. 9-11). With transvaginal color Doppler imaging, placental blood flow within the periphery of the complex adnexal massâ€"the *ring of fire* â€"can be seen (Fig. 7-7). Although this can help to make the diagnosis, this finding can also be seen with a corpus luteum of pregnancy (Pellerito, 1992). Pulsed-color Doppler sonographic measurements of resistance indices have been reported to help differentiate between a corpus luteal cyst and ectopic pregnancy, although poor sensitivity limits their utility (Atri, 2003a).

FIGURE 7-7



Color Doppler transvaginal sonography of an ectopic pregnancy. The "ring of fire" reflects placental blood flow around the periphery of the pregnancy. This finding, however, may also be seen with corpus luteum cysts. *(Courtesy of Dr. Elysia Moschos.)*

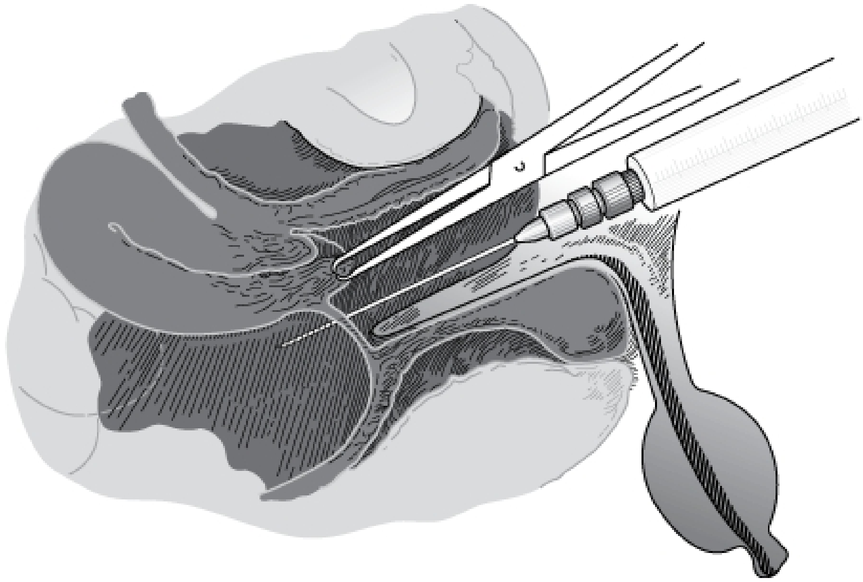
With evaluation of the pelvis, free peritoneal fluid suggests intra-abdominal bleeding. Although TVS can detect as little as 50 mL of fluid in the cul-de-sac of Douglas, transabdominal sonography helps assess the extent of hemoperitoneum. Moreover, detection of peritoneal fluid in conjunction with an adnexal mass is highly predictive of ectopic pregnancy (Nyberg, 1991).

Despite technological advances, the absence of suggestive findings does not exclude an ectopic pregnancy. In addition, TVS has not decreased the prevalence of tubal rupture or need for transfusions at the time of surgery (Atri, 2003b). However, sonography has decreased the need for diagnostic laparoscopy or curettage or both to establish the diagnosis of ectopic pregnancy. Condous and colleagues (2007) report vaginal sonography yielding the correct pre-operative diagnosis of ectopic pregnancy in nearly 91 percent of cases.

Culdocentesis

With a 16- to 18-gauge spinal needle, the cul-de-sac may be entered through the posterior vaginal fornix as upward traction is applied to the cervix with a tenaculum (Fig. 7-8). The characteristics of the aspirate, in conjunction with clinical findings, may help clarify the diagnosis. Normal-appearing peritoneal fluid is designated as a negative test. If fragments of an old clot or nonclotting blood are found in the aspirate when placed into a dry clean test tube, then hemoperitoneum is diagnosed. If the aspirated blood clots after it is withdrawn, this may signify active intraperitoneal bleeding or puncture of an adjacent vessel. If fluid cannot be aspirated, the test can only be interpreted as unsatisfactory. Finally, purulent fluid suggests a number of infection-related causes such as salpingitis or appendicitis. There also are a number of nongynecologic findings, for example, fat necrosis from pancreatitis and feculent material from a perforated or ruptured colon or an inadvertent puncture of the rectosigmoid colon.

FIGURE 7-8



Culdocentesis. *(From Nichols, 1993, with permission.)*

Historically, culdocentesis was considered an easy bedside test used to diagnose hemoperitoneum, but a number of studies contradict its usefulness. Culdocentesis has been largely replaced by TVS (Glezerman, 1992; Vermesh, 1990). Sonographic findings of echogenic fluid to establish hemoperitoneum is more sensitive and specific than culdocentesisâ€"100 and 100 percent versus 66 and 80 percent, respectively. In addition, for most women, sonography is better tolerated.

Endometrial Sampling

There are a number of endometrial changes associated with ectopic pregnancy that include decidual reactions found in 42 percent of samples, secretory endometrium in 22 percent, and proliferative endometrium in 12 percent (Lopez, 1994). Trophoblasts are not seen. Barnhart and associates (2002) recommend that absence of trophoblastic tissue be confirmed by curettage before methotrexate treatment is given. They found that the presumptive diagnosis of ectopic pregnancy is inaccurate in nearly 40 percent of cases without histologic exclusion of a spontaneous pregnancy loss. Nevertheless, the need and method of endometrial sampling must carefully be weighed against the limited risks of methotrexate.

Pipelle biopsy was studied as an alternative to curettage and found inferior, with sensitivity of obtaining villi ranging from 30 to 63 percent (Barnhart, 2003b; Ries, 2000). By comparison, frozen section of curettage fragments to identify products of conception is accurate in over 90 percent of cases (Barak, 2005; Spandorfer, 1996).

Chorionic villi in specimens from women with the diagnosis of spontaneous abortion were identified clinically in only half of cases and by the pathologist in another 30 percent. Thus in 20 percent of women, an ectopic pregnancy was still a consideration (Lindahl, 1986).

Novel Serum Markers

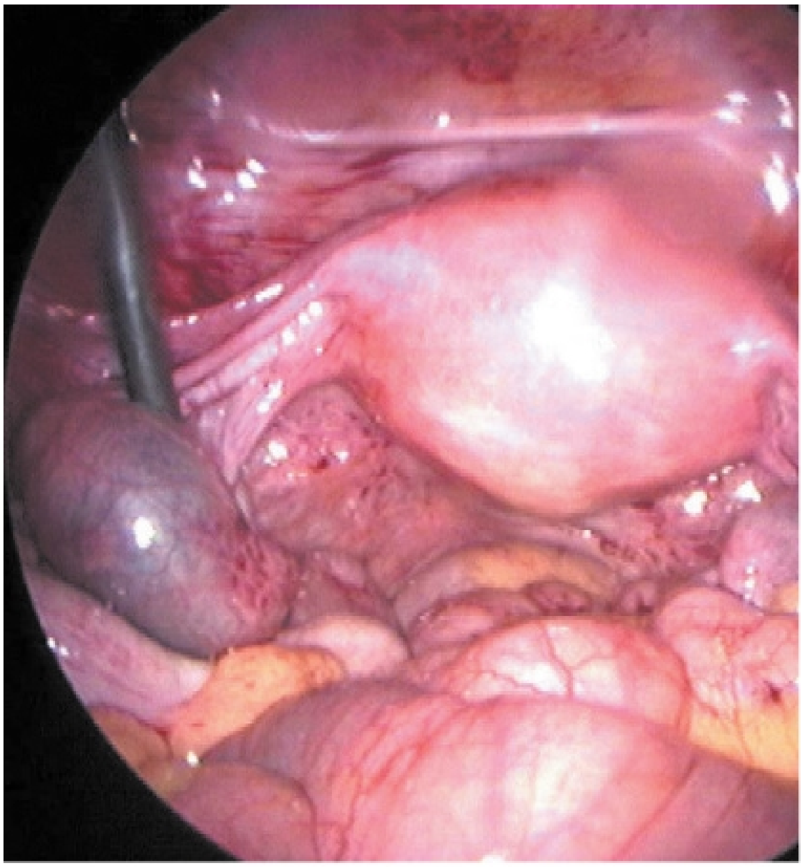
A number of small studies have been done to evaluate the utility of novel markers to detect ectopic pregnancy. Daniel and associates (1999) found that vascular endothelial growth factor (VEGF) in concentrations >200 pg/mL could differentiate between an ectopic and a normal or arrested uterine pregnancy with a sensitivity, specificity, and positive predictive value of 60, 90, and 86 percent, respectively. In addition, cancer antigen 125 (CA 125), serum creatine kinase, and fetal fibronectin concentrations have been investigated (Ness, 1998; Predanic, 2000). Recently, mass spectrometry-based proteomic techniques have also been used to

determine the biochemical blueprint of normal pregnancy and some of its disorders (Shankar, 2005).

SUMMARY OF DIAGNOSTIC EVALUATION

Confirmation by diagnostic laparoscopy remains the gold standard for diagnosis of ectopic pregnancy (Fig. 7-9). That said, with sensitive diagnostic modalities available, ectopic pregnancy can typically be diagnosed prior to surgery.

FIGURE 7-9



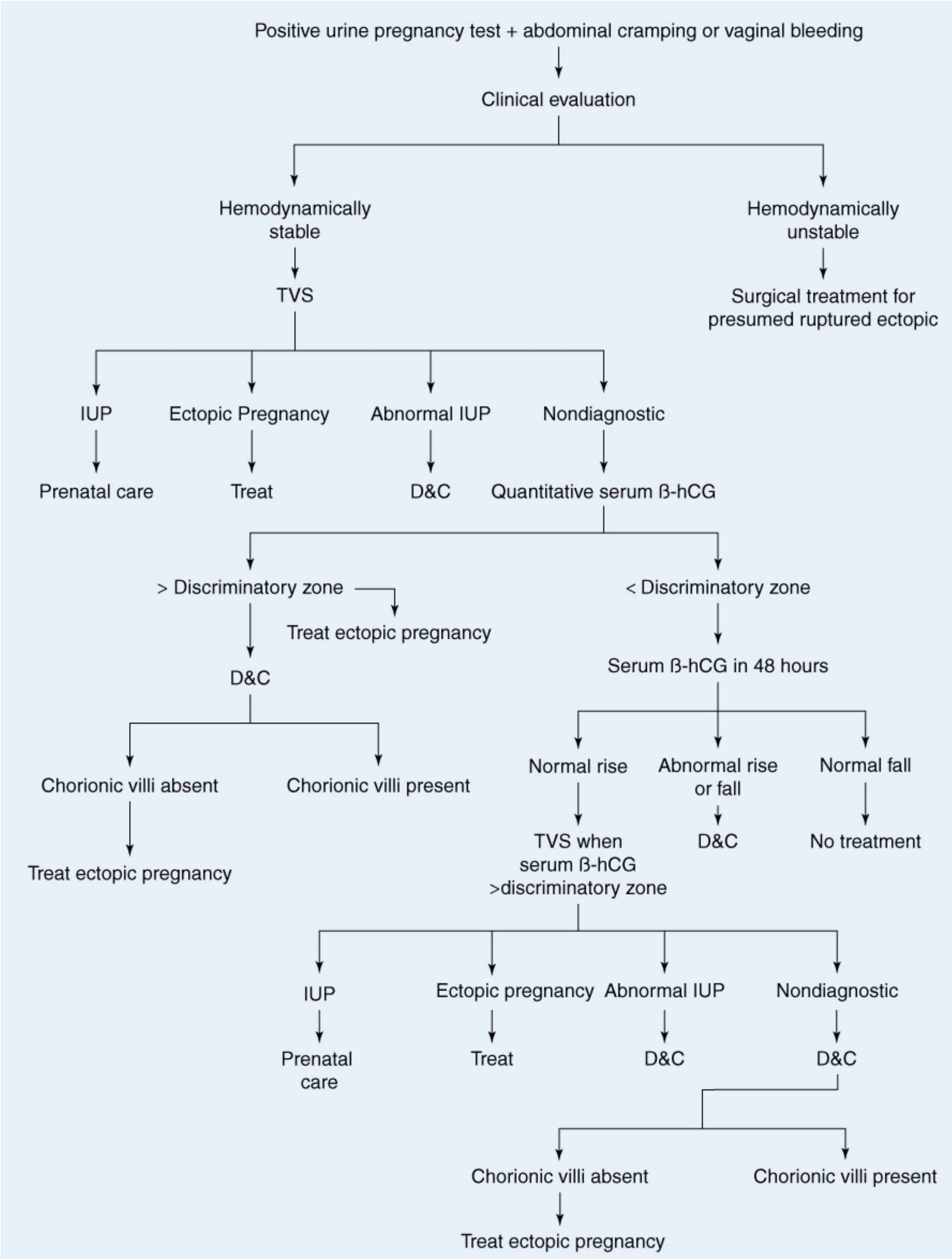
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Laparoscopic photograph. The blunt probe elevates a blue, distended left tubal ampulla. *(Courtesy of Dr. Kevin Doody.)*

Use of an evidence-based algorithm will facilitate identification of an ectopic pregnancy. After appropriate clinical evaluation, all reproductive-aged women with any suspicion of pregnancy should be tested using a sensitive urine β-hCG assay. Following positive testing, if an intrauterine pregnancy is not confirmed by sonography, no signs of acute intra-abdominal hemorrhage are present, and an ectopic gestation is suspected, then an evaluation such as the one depicted by the algorithm in Figure 7-10 may be used. Gracia and colleagues (2001) performed a decision analysis of six diagnostic strategies to evaluate which sequence of tests was most efficient in yielding the fewest missed ectopic pregnancies and interrupted uterine pregnancies. They found the best strategy to be TVS for all women with first-trimester pain or bleeding. If findings are not diagnostic, then serum β-hCG levels are measured. Using this strategy, only 1 percent of all potential uterine pregnancies were interrupted, no ectopic pregnancies were missed, and the average time to diagnosis was 1.5 days. In the event that overall sensitivity of available sonography for detecting uterine pregnancy is less than 93 percentâ€”because of older sonographic equipment, an inexperienced sonographer, patient obesity or discomfort, or distorted anatomyâ€—they recommend measurement of serum β-hCG levels first, reserving sonographic examination

for those women with levels above the discriminatory zone.

FIGURE 7-10



Positive urine pregnancy test + abdominal cramping or vaginal bleeding
Clinical evaluation
Hemodynamically stable
Hemodynamically unstable
TVS
Surgical treatment for presumed ruptured ectopic
IUP
Ectopic Pregnancy
Abnormal IUP
Nondiagnostic
Prenatal care
Treat
D&C
Quantitative serum ß-hCG
> Discriminatory zone
Treat ectopic pregnancy
< Discriminatory zone
D&C
Serum ß-hCG in 48 hours
Chorionic villi absent
Chorionic villi present
Normal rise
Abnormal rise or fall
Normal fall
Treat ectopic pregnancy
TVS when serum ß-hCG >discriminatory zone
D&C
No treatment
IUP
Ectopic pregnancy
Abnormal IUP
Nondiagnostic
Prenatal care
Treat
D&C
D&C
Chorionic villi absent
Chorionic villi present
Treat ectopic pregnancy

Algorithm of ectopic pregnancy evaluation. β-hCG = β-human chorionic gonadotropin; D&C = dilatation and curettage; IUP = intrauterine pregnancy; TVS = transvaginal sonography.

A hemodynamically stable woman with vaginal bleeding, a serum β-hCG level >2,000 IU/L, and no sonographic evidence for a uterine pregnancy is a good candidate for expectant management of presumed complete abortion. Serum β-hCG levels are repeated in 24 to 48 hours to elicit the trend of change (Condous, 2005). If the rate of decline is less than 20 percent at 2 days or 60 percent at 7 days, then completed spontaneous abortion is excluded, and persistence of trophoblastic tissue from either an incomplete miscarriage or an ectopic pregnancy must be assumed (Barnhart, 2004a).

MANAGEMENT

Without intervention, an ectopic tubal pregnancy can lead to tubal abortion, tubal rupture, or spontaneous resolution. Tubal abortion is the expulsion of products through the fimbrial end. This tissue can then either regress or reimplant in the abdominal cavity. With reimplantation, bleeding or pain necessitating surgical intervention is a common complication. Tubal rupture is associated with significant intra-abdominal hemorrhage.

Medical Management

Medical therapy is preferred by most, if feasible. Only methotrexate has been extensively studied as an alternative to surgical therapy. Other agents that have been used include prostaglandins and mifepristone, as well as potassium chloride or hyperosmolar glucose injected into the ectopic mass. The best candidate for medical therapy is a woman who is asymptomatic, motivated, and has the resources to be compliant with treatment surveillance. Absolute contraindications for medical therapy include hemodynamic instability, inability to remain compliant with posttherapeutic monitoring, intrauterine pregnancy, breast feeding, and clinically important hepatic/renal dysfunction (American Society for Reproductive Medicine, 2006). With medical therapy, some classic predictors of success include:

1. Initial serum β-hCG level: This is the single best prognostic indicator of treatment success in women given single-dose methotrexate. The prognostic value of the other two predictors may be directly related to their relationship with serum β-hCG concentrations. According to Lipscomb and colleagues (1999), an initial serum value <5,000 IU/L was associated with success rates of 92 percent, whereas an initial concentration >15,000 IU/L had success rates of 68 percent. In another study, Stika and colleagues (1996) reported that women with an initial β-hCG level >5,000 IU/L were more likely to require multiple doses of methotrexate or require surgical intervention.

2. Ectopic pregnancy size: Although there are few data concerning the effect of size on success rates with medical therapy, many early trials used "large size" as an exclusion criterion. In one study, success rates with single-dose methotrexate were 93 percent in cases with ectopic masses <3.5 cm, whereas success rates were between 87 and 90 percent when the mass was >3.5 cm (Lipscomb, 1998).

3. Fetal cardiac activity: Although identification of cardiac activity sonographically is a relative contraindication to medical therapy, this is based on limited evidence. Although most studies report an increased risk of failure if there is cardiac activity, success rates of 87 percent have been reported (Lipscomb, 1998).

METHOTREXATE

This is a folic acid antagonist that competitively inhibits the binding of dihydrofolic acid to dihydrofolate reductase, which in turn reduces the amount of the active intracellular metabolite, folinic acid. This leads to diminished nucleotide precursors and limited DNA synthesis (see Chap. 27, Methotrexate). It inhibits fast-growing tissue and is used for cancer chemotherapy in conditions such as gestational trophoblastic neoplasia and for early pregnancy termination. The drug can be given orally, intravenously, intramuscularly, or be directly injected into the ectopic pregnancy sac. Currently, parenteral methotrexate administration is used most commonly.

The most common side effects of methotrexate include stomatitis, conjunctivitis, and transient liver dysfunction, although myelosuppression, mucositis, pulmonary damage, and anaphylactoid reactions have been reported with only one dose of 50 to 100 mg (Isaacs, 1996; Straka, 2004). Although these side effects are seen in as many as a third of women treated, they are usually self-limited. In some cases, leucovorin (folinic acid) is given following treatment to blunt or reverse methotrexate side effects. Such therapy is termed *leucovorin rescue* .

The single-dose and multi-dose methotrexate protocols shown in Table 7-3 are associated with overall resolution rates for ectopic pregnancy of about 90 percent. There are no randomized trials comparing single-dose versus multidose administrations. Lipscomb and colleagues (2005) reviewed their institutional experience with methotrexate therapy in 643 consecutively treated patients. They found no differences in treatment duration, serum β-hCG levels, or success rates between the multidose and single-dose protocols, 95 and 90 percent, respectively. Barnhart and Gosman (2003a) performed a meta-analysis of 26 studies that included 1,327 women treated with methotrexate for an ectopic pregnancy. Single-dose therapy was more commonly used because of simplicity. It was found to be less expensive, was easily accepted because of less intensive post-therapy monitoring, and did not require leucovorin rescue (Alexander, 1996). The major drawback was that multidose treatment had a fivefold greater chance of success than single-dose therapy (OR 4.74; CI 1.77, 12.62). Failures included women with tubal rupture, massive intra-abdominal hemorrhage, need for urgent surgery, and blood transfusions. Ultimately, most women received between one and four doses of methotrexate. Both regimens had similar side effects.

Table 7-3 Medical Treatment Protocols for Ectopic Pregnancy

	Single Dose	**Two dose**	**Multidose**
Dosing	One dose; repeat if necessary	Days 0 and 4	Up to four doses of both drugs until serum β-hCG declines by 15%
Medication Dosage			
Methotrexate	50 mg/m^2 BSA (day 1)	50 mg/m2 BSA	1 mg/kg, days 1, 3, 5, and 7
Leucovorin	N/A	N/A	0.1 mg/kg days 2, 4, 6, and 8
Serum b-hCG level	Days 0 (baseline), 4, and 7	Days 0 (baseline),4, and 7 Days 11 and 14 if repeat dose is given	Days 0 (baseline), 1, 3, 5, and 7
Indication for additional dose	■ If serum β-hCG level does not decline by 15% from day 4 to day 7 ■ Less than 15% decline during weekly surveillance	■ If serum β-hCG does not decline by 15% from day 4 to day 7 ■ If serum β-hCG does not decline by 15% from day 7 to day 11 ■ Maximum of four doses	If serum β-hCG declines <15%, give additional dose; repeat serum β-hCG in 48 hours and compare with previous value; maximum four doses
Posttherapy surveillance	Weekly until serum β-hCG undetectable	Weekly until serum β-hCG undetectable	Weekly until serum β-hCG undetectable

BSA = body surface area; β-hCG = β-human chorionic gonadotropin; N/A = not applicable.

In the only randomized clinical trial comparing single and multidose therapy, success rates between both treatment groups were similar (89 and 93 percent respectively) (Alleyassin, 2006). Given the convenience and efficacy, we use single dose methotrexate.

Single-Dose Methotrexate

Intramuscular methotrexate given as a single dose has been the most widely used medical treatment of ectopic pregnancy. A variety of doses has been studied, and the most popular is the 50 mg/m^2 body surface area (BSA) protocol described by the group from Memphis (Stovall, 1993). In the small randomized trial by Hajenius and colleagues (2000), treatment with 25 mg/m^2 was

equally effective as treatment with 50 mg/m^2 . Table 27-2 can be used to calculate BSA.

Close monitoring is imperative. A baseline serum β-hCG level is determined prior to methotrexate administration (Day 0). Treatment is considered Day 1 and serum β-hCG levels are repeated on days 4 and 7 following injection. Levels usually continue to rise until day 4. Of note, the serum β-hCG level on day 4 does not correlate with success of medical therapy or the need for future surgery. Comparison is then made between day 4 and 7 serum values. If there is a decline by 15 percent or more, weekly serum β-hCG levels are drawn until they measure <15 IU/L. A decline of less than 15 percent is seen in approximately 20 percent of treated women. In such cases, a second 50-mg/m^2 dose is given and the protocol repeated. Approximate time to resolution for all women averages 36 days, but in some treatment required 109 days (Lipscomb, 1998).

During the first few days following methotrexate administration, up to half of women experience a short duration of abdominal pain that can be controlled with nonsteroidal anti-inflammatory drugs. This *separation pain* presumably results from tubal distention caused by tubal abortion or hematoma formation or both (Stovall, 1993). In some cases, inpatient observation with serial hematocrit determinations and gentle abdominal examinations help assess the need for surgical intervention. Sonographic monitoring of ectopic mass dimensions can be misleading after serum β-hCG levels have declined to <15 IU/L. Brown and colleagues (1991) have described persistent masses to be resolving hematomas rather than persistent trophoblastic tissue.

Multidose Methotrexate

The most common regimen is seen in Table 7-3 and consists of up to four doses of parenteral methotrexate, followed by adjunctive doses of leucovorin 24 hours later. Serial serum β-hCG concentrations are obtained. If there is not a 15-percent decline from the previous valueâ€”for example, days 0 to 1 or days 1 to 3â€”an additional methotrexate/leucovorin dose is given, and the serum β-hCG level is repeated 2 days later. A maximum of four doses are given and weekly serum β-hCG surveillance continues until values are undetectable.

In an attempt to maximize the balance between efficacy and convenience for women undergoing methotrexate therapy for an ectopic pregnancy, Barnhart and co-workers (2007) have recently described a hybrid two-dose protocol. The preliminary study supports the safety of administering two doses of methotrexate without leucovorin rescue on days 0 and 4. Larger studies are required to confirm equivalent effectiveness.

Oral Methotrexate

Bioavailability of oral and parenteral methotrexate is similar (Jundt, 1993). There are only a few trials in which oral methotrexate was evaluated. Korhonen and colleagues (1996) randomly assigned women with tubal pregnancies without cardiac activity and serum β-hCG levels <5,000 IU/L to receive low-dose oral methotrexate, 2.5 mg daily for 5 days, or to be managed expectantly and found no differences in primary treatment success. Bengtsson and associates (1992) gave 15 mg of methotrexate orally on days 1, 3, and 5 with folinic acid on days 2, 4, and 6. This was successful in 14 of 15 women with a mean resolution time of 24 days.

Mifepristone Plus Methotrexate

It seems logical that the addition of 600 mg of mifepristone orally to single-dose methotrexate might improve efficacy and result in faster resolution of the unruptured ectopic pregnancy (see Chap. 6, Medical Abortion). In a randomized trial of 212 cases, however, Rozenberg and co-workers (2003) documented no differences in success rates.

DIRECT INJECTION INTO ECTOPIC PREGNANCY

Methotrexate

In efforts to minimize systemic side effects of methotrexate, local injection into the gestational sac under sonographic or laparoscopic guidance has been evaluated. Pharmacokinetic studies with 1 mg/kg of methotrexate injected either into the sac or intramuscularly showed similar success rates but fewer side effects with intragestational injection (Fernandez, 1994).

Hyperosmolar Glucose

In a small prospective trial, Yeko and colleagues (1995) reported that direct injection of 50-percent glucose into the ectopic mass using laparoscopic guidance was 94 percent successful in women with an unruptured ectopic whose serum β-hCG level was <2,500 IU/L. Gjelland and co-workers (1995) reported that treatment success was significantly better in a similar population in whom

sonographic- rather than laparoscopic-guided injection was used.

SURVEILLANCE

Posttherapy monitoring assesses treatment success and screens for signs of persistent ectopic pregnancy. Most medical management protocols have well-defined surveillance schedules. Kirk and colleagues (2007) prospectively tested the "day four to seven" rule in an attempt to predict success at an earlier stage and ultimately found it superior to all other combinations. In the absence of symptoms, bimanual examinations are limited to avoid theoretical risk of tubal rupture. Posttherapy sonography is reserved for suspected complications such as tubal rupture. Likewise, repeated liver function tests were not useful in the face of normal pretreatment values because very few clinically relevant abnormalities are detected (Lecuru, 2000). Most recommend contraception for 3 to 6 months after successful medical therapy with methotrexate, as this drug may persist in human tissues for up to 8 months after a single dose (Warkany, 1978).

Surgical Management

LAPAROTOMY VERSUS LAPAROSCOPY

There have been at least three prospective studies that compared open laparotomy with laparoscopic surgery for ectopic pregnancies (Lundorff, 1991; Murphy, 1992; Vermesh, 1989). Their findings are summarized below:

1. There were no significant differences in overall tubal patency determined at second-look laparoscopy. This was despite higher rates of ipsilateral adhesions in the laparotomy group.
2. Each method was followed by a similar number of subsequent uterine pregnancies.
3. There were fewer subsequent ectopic pregnancies in women treated laparoscopically, although this was not significant.
4. Laparoscopy resulted in shorter operative times, less blood loss, less analgesic requirement, and shorter hospital stays.
5. Laparoscopic surgery was significantly less successful in resolving the tubal pregnancy (RR 0.90; CI 0.83, 0.97). However, this was balanced by the above-mentioned benefits of laparoscopy.
6. The costs for laparoscopy were significantly less than for laparotomy, although some argue that costs are similar when cases converted to laparotomy are considered (Foulk, 1996).

Since completion of these studies, with improvements in laparoscopic equipment and with accrued experience, cases previously managed by laparotomy such as ruptured tubal or intact interstitial pregnancies, can now be more safely approached using laparoscopy than before (Sagiv, 2001).

LAPAROSCOPY

To date there have been no randomized trials to guide the choice between conservative (salpingostomy) and radical (salpingectomy) procedures done via laparoscopy. Retrospective reviews show equivalent subsequent uterine pregnancy rates for both conservative and radical surgery for tubal pregnancyâ€”46 and 44 percent (Clausen, 1996). Recurrent ectopic pregnancy rates are slightly higher in women having radical surgery compared with conservative techniquesâ€”15 versus 10 percent.

SALPINGECTOMY

If the contralateral fallopian tube appears normal, then salpingectomy is a reasonable treatment option that avoids the 5 to 8 percent complication rate caused by persistent or recurrent ectopic pregnancy in the same tube (Rulin, 1995). A surgical description is found in Sections 41-25, Salpingectomy and Salpingostomy and 41-30, Laparoscopic Salpingectomy.

SALPINGOSTOMY

The woman who is hemodynamically stable and strongly desires to preserve fertility is an appropriate candidate for salpingostomy. With salpingostomy, retrospective study by Milad and colleagues (1998) indicates that ectopic resolution rates were lower in women in whom the initial serum β-hCG level was <8,000 IU/L. Supportive evidence for this comes from Natale and associates (2003), who reported that serum β-hCG levels >6,000 mIU/mL have a high risk of implantation into the tubal muscular layer with subsequent tubal damage.

Medical versus Surgical Therapy

There are a number of randomized trials that have compared methotrexate treatment with laparoscopic surgery. One multicenter trial compared a multidose methotrexate protocol with laparoscopic salpingostomy and found no differences for tubal preservation and primary treatment success (Hajenius, 1997). Health-related quality of lifeâ€”pain, posttherapy depression, and decreased perception of healthâ€”was significantly impaired after systemic methotrexate compared with laparoscopic salpingostomy (Nieuwkerk, 1998). And, 61 percent of women undergoing medical therapy experienced methotrexate complications.

In comparison, single-dose methotrexate was overall less successful in resolving pregnancy than laparoscopic salpingostomy (RR 0.83; CI 0.71, 0.97), although tubal patency and subsequent uterine pregnancy were similar between both groups (Fernandez, 1998; Sowter, 2001). Women treated with methotrexate had significantly better physical functioning immediately following therapy, but there were no differences in psychological functioning.

All things considered, future reproductive potential, as defined by contralateral fallopian tube patency and subsequent intrauterine pregnancies, are similar after medical and surgical therapy (Buster and Krotz, 2007; Elito, 2006). In addition, recurrent ectopic pregnancy rates are comparable (8 percent to 13 percent) after the currently accepted methods of treatment (Buster and Krotz, 2007).

From the above, we conclude that women who are hemodynamically stable and in whom there is a small tubal diameter, no fetal cardiac activity, and serum β-hCG concentrations <5,000 IU/L have similar outcomes with medical or surgical management. Despite lower success rates with medical therapy for women with larger tubal size, higher serum β-hCG levels, and fetal cardiac activity, medical management can be offered to a motivated woman who understands the risks of emergency surgery in the event of treatment failure.

Expectant Management

In select women, some choose close observation in the event that there will be spontaneous resorption of an ectopic pregnancy. Intuitively, it is difficult to accurately predict which woman will have an uncomplicated course with such management. Although an initial serum β-hCG concentration has been shown to best predict outcome, the range varies widely. For example, initial values of <200 IU/L predict successful spontaneous resolution in 88 to 96 percent of attempts, whereas values >2,000 IU/L had success rates of only 20 to 25 percent (Elson, 2004; Trio, 1995). Even with declining values, when the initial β-hCG level exceeded 2,000 IU/L, the success rate was only 7 percent (Shalev, 1995). Interestingly, there was no difference in ipsilateral tubal patency or 1-year fertility rates with either success or failure of expectant management. Close monitoring is warranted because of reports of tubal rupture despite low and declining serum β-hCG levels. An argument could be made that minimal side effects of methotrexate make it preferable to avoid the prolonged surveillance and associated patient anxiety.

Persistent Ectopic Pregnancy

Abdominal pain after conservative surgical management of a tubal pregnancy should prompt immediate suspicion for persistent trophoblast proliferation. Incomplete removal of trophoblastic tissue and its continued growth causes tubal rupture in 3 to 20 percent of women (Graczykowski, 1999). Perhaps ironically, persistent ectopic pregnancy is more likely with very early pregnancies. Specifically, surgical management is more difficult because pregnancies smaller than 2 cm are harder to visualize and completely remove. To obviate this, Graczykowski and associates (1997) administered a prophylactic dose of 1 mg/m^2 methotrexate postoperatively, which reduced the incidence of persistent ectopic pregnancy as well as length of surveillance.

The optimal schedule to identify persistent ectopic pregnancy after surgical therapy has not been determined. Protocols describe serum β-hCG level monitoring from every 3 days to every 2 weeks. Spandorfer and associates (1997) estimated the risk of persistent ectopic pregnancy based on serum β-hCG levels done on the first postoperative day. They observed that if serum β-hCG levels fell by >50 percent compared with presurgical values, then there were no treatment failures within the first 9 days, and thus subsequent serum β-hCG determinations 1 week after surgery were appropriate. Conversely, if serum levels fell by <50 percent then there was a 3.5-fold increased risk of failure within the first week, thus necessitating earlier follow-up. Importantly, despite low and falling serum β-hCG concentrations, tubal rupture can still occur (Tulandi, 1991).

Currently, standard therapy for persistent ectopic pregnancy is single-dose methotrexate with 50 mg/m^2 BSA. Although considered,

there have been few studies to evaluate low-dose oral methotrexate for these. Bengtsson and colleagues (1992) gave 15 mg of methotrexate orally on days 1, 3, and 5, with folinic acid 30 mg on days 2, 4, and 6, and found this regimen effective in 14 of 15 women enrolled in their study.

Anti-D Isoimmunization

If the woman is D-negative and her partner has a blood group that is either D-positive or unknown, then 300 µg anti-D immune globulin should be given intramuscularly to prevent anti-D isoimmunization.

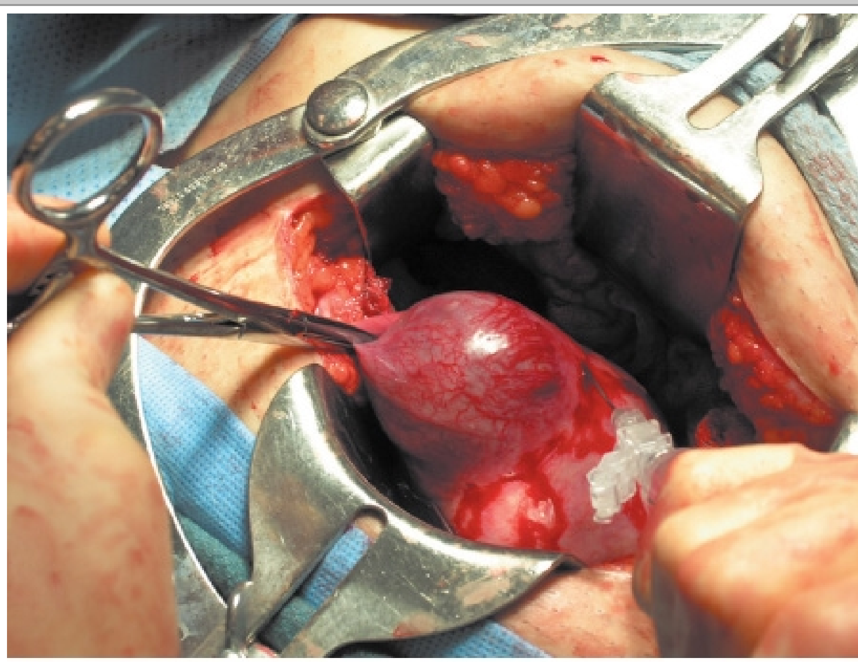
OVARIAN PREGNANCY

Ectopic implantation of the fertilized egg in the ovary is rare. The recent increased incidence likely is artifactual due to improved imaging modalities. Risk factors are similar to those for tubal pregnancies. In one study, IUD users had a higher proportion of ovarian pregnancies compared with non-usersâ€”5.5 percent versus none (World Health Organization, 1985). Nearly a third of women with an ovarian pregnancy present with hemodynamic instability because of rupture. Diagnosis is based on the classic sonographic description of a cyst with a wide echogenic outer ring on or within the ovary (Comstock, 2005).

INTERSTITIAL PREGNANCY

Also termed cornual pregnancy, interstitial pregnancies implant in the proximal tubal segment that lies within the muscular uterine wall. Swelling lateral to the insertion of the round ligament is the characteristic anatomic finding (Fig. 7-11). In the past, rupture usually followed 8 to 16 weeks of amenorrhea because of the greater distensibility of the myometrium covering the interstitial segment of fallopian tube. Risk factors are similar to others discussed, although previous ipsilateral salpingectomy is a specific risk factor for interstitial pregnancy (Lau, 1999). Because of the proximity of these pregnancies to the uterine and ovarian arteries, there is a risk of severe hemorrhage (Tulandi, 2004).

FIGURE 7-11



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Interstitial pregnancy. Lateral to the cornua, a pean clamp holds the fallopian tube and utero-ovarian ligament. Diluted vasopressin is injected at the pregnancy base to minimize bleeding during resection. *(Courtesy of Dr. Marlene Corton.)*

Using TVS and serum β-hCG assays as discussed for suspected tubal pregnancy, interstitial pregnancy can be diagnosed early enough to allow conservative medical or surgical therapy (Bernstein, 2001). Given the low incidence of interstitial pregnancy, no consensus regarding prediction of success using methotrexate has been established. Jermy and colleagues (2004) reported a 94 percent success rate with systemic methotrexate using 50 mg/m^2 BSA. Their series included four women in whom cardiac activity was verified. Because these women have higher initial serum β-hCG levels at diagnosis, longer surveillance is usually needed. Deruelle and co-workers (2005) advocate postmethotrexate treatment selective uterine artery embolization to help avert the risk of hemorrhage and hopefully hasten ectopic pregnancy resolution.

Surgical management involves cornual resection either at laparotomy or laparoscopy. Hysteroscopic resection of an interstitial pregnancy has been described by Sanz and Verosko (2002), but long-term results following this technique are unknown.

The risk of uterine rupture with subsequent pregnancies following either medical or conservative surgical management is unclear. Thus, careful observation of these women, along with consideration of elective cesarean delivery, is warranted.

CERVICAL PREGNANCY

The incidence of cervical pregnancy is reported to be between 1 in 8,600 to 12,400 pregnancies (Ushakov, 1997). The incidence appears to be rising because of assisted reproductive technology, especially in vitro fertilization and embryo transfer (Ginsburg, 1994; Pattinson, 1994). A risk factor unique to cervical pregnancy is a history of dilation and curettage, seen in nearly 70 percent of cases (Hung, 1996; Pisarska, 1999). Two diagnostic criteria are necessary for confirmation of cervical pregnancy: (1) the presence of cervical glands opposite the placental attachment site, and (2) a portion of or the entire placenta must be located below either the entrance of the uterine vessels or the peritoneal reflection on the anterior and posterior uterine surface.

Early diagnosis of cervical pregnancy may obviate uncontrollable hemorrhage and subsequent hysterectomy in these women. Because of its rarity, experiences with medical therapy of cervical pregnancy are limited. Systemic or intra-amnionic instillation of methotrexate was reported effective in a few cases (Hung, 1996; Kung, 1997). Surgical management involves cervical suction curettage and control of hemorrhage using Sturmdorf sutures. Because of the morbidity associated with surgical therapy, medical therapy is usually given if there is no serious bleeding at the time of discovery. In a recent report, Mesogitis and colleagues (2005) described nine women in whom 25-mg dose of methotrexate was injected directly into the amnionic sac. After documentation of trophoblastic tissue regression, cervical suction curettage was successful in all. In the event of hemorrhage, a 26-F Foley catheter with a 30-mL balloon can be placed intracervically and inflated to effect hemostasis and to monitor uterine drainage. The balloon remains inflated for 24 to 48 hours and is gradually decompressed over the next few days (Ushakov, 1997). Bilateral uterine artery embolization has also been successfully used to avert acute hemorrhage after involution and detachment of the cervical pregnancy (Trambert, 2005).

HETEROTOPIC PREGNANCY

A uterine pregnancy in conjunction with an extrauterine pregnancy is termed *heterotopic pregnancy* . In the past, incidence estimates were computed to be 1 in 30,000 pregnancies, figuring incidences of dizygotic twinning and ectopic pregnancy of 1 percent each. As a result of assisted reproductive technology, the rate of heterotopic pregnancies has literally skyrocketed to 1 in 100 pregnancies (Habana, 2000). Mechanisms that have been proposed to explain this include hydrostatic forces delivering the embryo into the cornual or tubal area, the tip of the catheter directing transfer towards the tubal ostia, or reflux of uterine secretions leading to retrograde tubal implantation.

When a tubal pregnancy coexists with a uterine pregnancy, potassium chloride can be injected into the tubal pregnancy sac. Methotrexate is contraindicated due to the detrimental effects on the normal pregnancy. Cases of craniofacial, skeletal, cardiopulmonary, and gastrointestinal anomalies have been described even with limited first-trimester methotrexate exposure (Nguyen, 2002).

CESAREAN DELIVERY SCAR PREGNANCY

Implantation within the scar of a previous cesarean delivery through a microscopic tract in the myometrium represents a rare condition carrying serious maternal morbidity and mortality from massive hemorrhage. Differentiating between a cervico-isthmic pregnancy and a cesarean delivery scar pregnancy can be difficult. According to Godin (1997), there are four sonographic criteria that must be met to secure the diagnosis: (1) an empty uterine cavity, (2) an empty cervical canal, (3) a gestational sac in the anterior part of the uterine isthmus, and (4) absence of healthy myometrium between the bladder and gestational sac. Imaging with three-dimensional color Doppler imaging provides an appreciation of the uteroplacental vascularization pattern (Chou, 2004). Also, magnetic resonance imaging can aid in the evaluation. Treatment using methotrexate, laparoscopic resection, or laparotomy is situationally dependent. Given the reportedly prolonged duration necessary to achieve complete resolution with medical treatmentâ€”3 to 4 monthsâ€”definitive devascularization might be expedited with addition of uterine artery embolization.

PREVENTION

Ectopic pregnancy is difficult to prevent because risk factors are poorly modified (Butts, 2003). Tubal pathology carries one of the highest risks and pelvic inflammatory disease plays a major role in tubal adhesions and obstruction. Because chlamydial infections constitute nearly half of pelvic inflammatory disease cases, efforts have been directed towards screening high-risk populations for asymptomatic infections (see Table 1-2). These include sexually active women under the age of 25 or women who use nonbarrier forms of contraception. Such screening programs in Sweden have demonstrated steady declines in both chlamydial infections and ectopic pregnancy rates, especially in women aged 20 to 24 years (Cates, 1999; Egger, 1998).

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ABNORMAL UTERINE BLEEDING: INTRODUCTION

Regular cyclic menstruation results from the choreographed relationship between the endometrium and its regulating factors (see Chap. 15, Histologic Menstrual Cycle Changes). Changes in either of these frequently results in abnormal bleeding. Causes of this bleeding may include neoplastic growth, hormonal dysfunction, reproductive-tract trauma, infection, coagulopathies, and complications of pregnancy. As a result, abnormal uterine bleeding is a common gynecologic complaint that may affect females of all ages.

DEFINITIONS

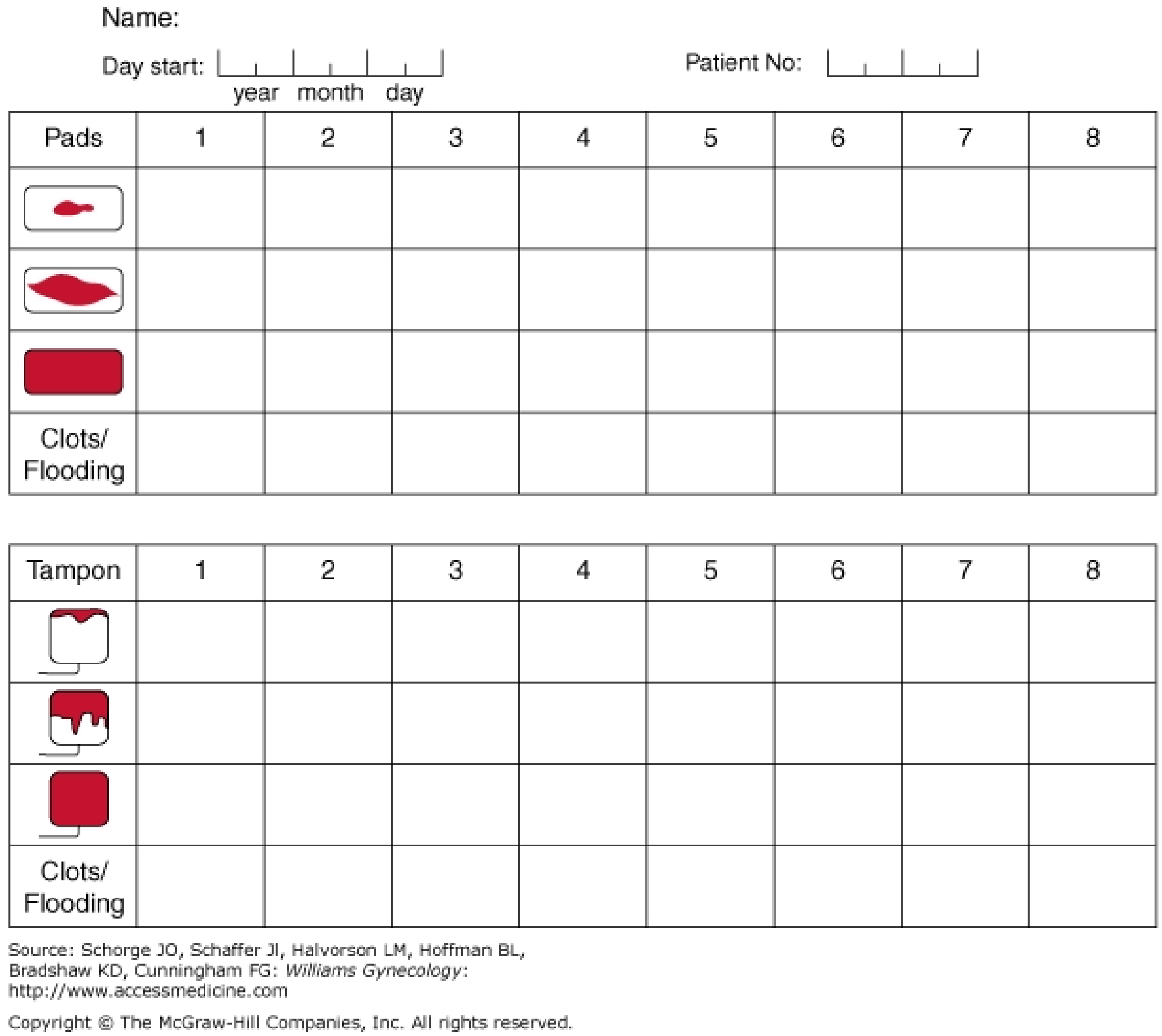
Abnormal bleeding may display several patterns. *Menorrhagia* is defined as prolonged or heavy cyclic menstruation. Objectively, menses lasting longer than 7 days or exceeding 80 mL of blood loss are determining values (Hallberg, 1966). *Metrorrhagia* describes intermenstrual bleeding. The term *breakthrough bleeding* is a more informal term for metrorrhagia that accompanies hormone administration. Frequently women may complain of both patterns, *menometrorrhagia* . In some women, there is diminished flow or shortening of menses, *hypomenorrhea* . Normal menstruation typically occurs every 28 days Â± 7 days. Cycles with intervals longer than 35 days describe a state of *oligomenorrhea* . Finally, the term *withdrawal bleeding* refers to the predictable bleeding that often results from abrupt progestin cessation.

Assessing heavy bleeding in a clinical setting has its limitations. For example, several studies have documented the lack of correlation between patient perception of blood loss and objective measurement (Chimbira, 1980c; Fraser, 1984). As a result, methods to objectively assess blood loss have been investigated. Hallberg and associates (1966) describe a technique to extract hemoglobin from sanitary napkins using sodium hydroxide. Hemoglobin is converted to hematin and can be measured spectrophotometrically. The constraints to this approach in a clinical setting are obvious.

Other tools used to estimate menstrual blood loss include hemoglobin and hematocrit evaluation. Hemoglobin concentration <12 g/dL increases the chance of identifying women with menorrhagia. A normal level, however, does not exclude menorrhagia, as many women with clinically significant bleeding have normal values.

Another method involves estimating of the number and type of pads used by a woman during menses. Warner and colleagues (2004) found positive correlations between objective menorrhagia with passing clots more than 1.1 inches in diameter and changing pads more frequently than every 3 hours. Attempts to standardize this type of evaluation have lead to development of the pictorial blood assessment chart (Fig. 8-1). Scores are assigned as follows: 1 point for each lightly stained tampon, 5 if moderately saturated, and 10 if completely soaked. Pads are similarly given ascending scores of 1, 5, and 20, respectively. Small clots score 1 point, whereas large clots score 5. Totals more than 100 points per menstrual cycle have been shown to indicate >80-mL objective blood loss (Higham, 1990; Janssen, 1995; Reid, 2000).

FIGURE 8-1



The pictorial bleeding assessment chart. Patients are counseled to evaluate the degree of saturation for each sanitary product used during menstruation. The total number of each type of sanitary product is then listed in the corresponding row during each day of menstruation. See text for assignment of points to each sanitary product and for calculation of total points. *(From Higham, 1990, with permission.)*

INCIDENCE

Abnormal uterine bleeding affects 10 to 30 percent of reproductive-aged women and up to 50 percent of perimenopausal women (Haynes, 1977; Prentice, 2000). Factors that impact the incidence most greatly are age and reproductive status. For example, uterine bleeding is uncommon in prepubertal girls and menopausal women, whereas rates of abnormal bleeding increase significantly in adolescent, perimenopausal, and reproductive-age groups. Familiarity with the most common etiologies of bleeding within these demographics often aids diagnosis and treatment (Table 8-1).

Table 8-1 Differential Diagnosis of Abnormal Bleeding

Dysfunctional uterine bleeding
Anovulatory
Perimenarchealâ€”immature hypothalamic-pituitary-ovarian axis
Perimenopausalâ€”insensitive ovarian follicles
Endocrinopathiesâ€”see systemic causes
Drugsâ€”hypothalamic depressants, steroids
Ovulatory
Organic lesions
Pregnancy-associated causesâ€”implantation spotting, abortion, ectopic pregnancy, gestational trophoblastic disease, postabortal or postpartum infection
Anatomic uterine lesions
Neoplasmâ€”leiomyoma, polyp, endometrial hyperplasia, cancer
Atrophic endometrium
Infectionâ€”sexually transmitted disease, tuberculosis
Mechanical causesâ€”intrauterine device, perforation
Arteriovenous malformation
Partial outflow obstructionâ€”congenital mÃ¼llerian defect, Asherman syndrome
Anatomic nonuterine lesions
Ovarian lesionsâ€”hormonally functional neoplasm
Fallopian tube lesionsâ€”salpingitis, cancer
Cervical and vaginal lesionsâ€”cancer, polyp, infection, atrophic vaginitis, foreign body, trauma
Systemic abnormalities
Exogenous hormone administrationâ€”sex steroids, corticosteroids
Coagulopathies
Hepatic failure
Chronic renal failure
Endocrinopathiesâ€”hypothyroidism, hyperthyroidism, adrenal disorders, diabetes mellitus, hypothalamic-pituitary disorders, polycystic ovarian syndrome, obesity

Adapted from Leiserowitz, 1996, with permission.

Childhood

Bleeding prior to menarche should be investigated as an abnormal finding. Initial evaluation should focus on determining the location of the bleeding, because vaginal, rectal, or urethral bleeding can present similarly. In this age group, the vagina, rather than the uterus, is the most common source of bleeding. Vulvovaginitis is the most frequent cause, but dermatologic conditions, neoplastic growths, or trauma by accident, abuse, or foreign body may also be reasons. In addition to vaginal sources, bleeding may also originate from the urethra and may reflect urethral prolapse or infection.

True uterine bleeding usually is caused by increased estrogen levels. Precocious puberty, accidental exogenous ingestion, or ovarian neoplasms should be considered in these children. Because of the risks associated with these, pelvic examination is requisite to identify the source as vaginal or uterine (Quint, 2001).

Adolescence

Abnormal uterine bleeding in adolescents results from anovulation and coagulation defects at disproportionately higher rates compared with older reproductive-aged women (Claessens, 1981; Oral, 2002; Smith, 1998). In contrast, neoplastic growths such as polyps, leiomyomas, and ovarian neoplasms are less frequent. Importantly, pregnancy, sexually transmitted diseases, and sexual abuse should not be ignored in this population.

Reproductive Age

Menorrhagia is a frequent problem in reproductive-aged women. It is estimated that a woman has a 1 in 20 lifetime chance of consulting her primary physician because of menorrhagia (Bongers, 2004).

Following adolescence, the hypothalamic-pituitary-ovarian axis matures and anovulatory uterine bleeding is encountered less frequently. With increased sexual activity, bleeding related to pregnancy and sexually transmitted disease increases. The incidence of leiomyomas and endometrial polyps increases with age, and thus bleeding from these lesions becomes common in older reproductive aged women.

Perimenopause

Abnormal uterine bleeding is a frequent clinical problem, accounting for 70 percent of all gynecologic visits by peri- and postmenopausal women. As with perimenarchal girls, anovulatory uterine bleeding from dysfunction of the hypothalamic-pituitary-ovarian axis becomes a more common finding in this group. Alternatively, the incidence of bleeding related to pregnancy and sexually transmitted disease decreases. With increasing age, there are greater risks of benign and malignant neoplastic growth. For example, Seltzer and colleagues (1990) reviewed the charts of 500 perimenopausal women and characterized alterations in their menstrual flow. They found that 18 percent had menorrhagia or metrorrhagia and one fifth of these were due to premalignant or malignant disease.

Menopause

Bleeding after menopause typically originates from benign disease. For example, Choo and colleagues (1985) found that the majority of cases resulted from atrophy of the endometrium. Benign endometrial polyps may also cause bleeding in this population.

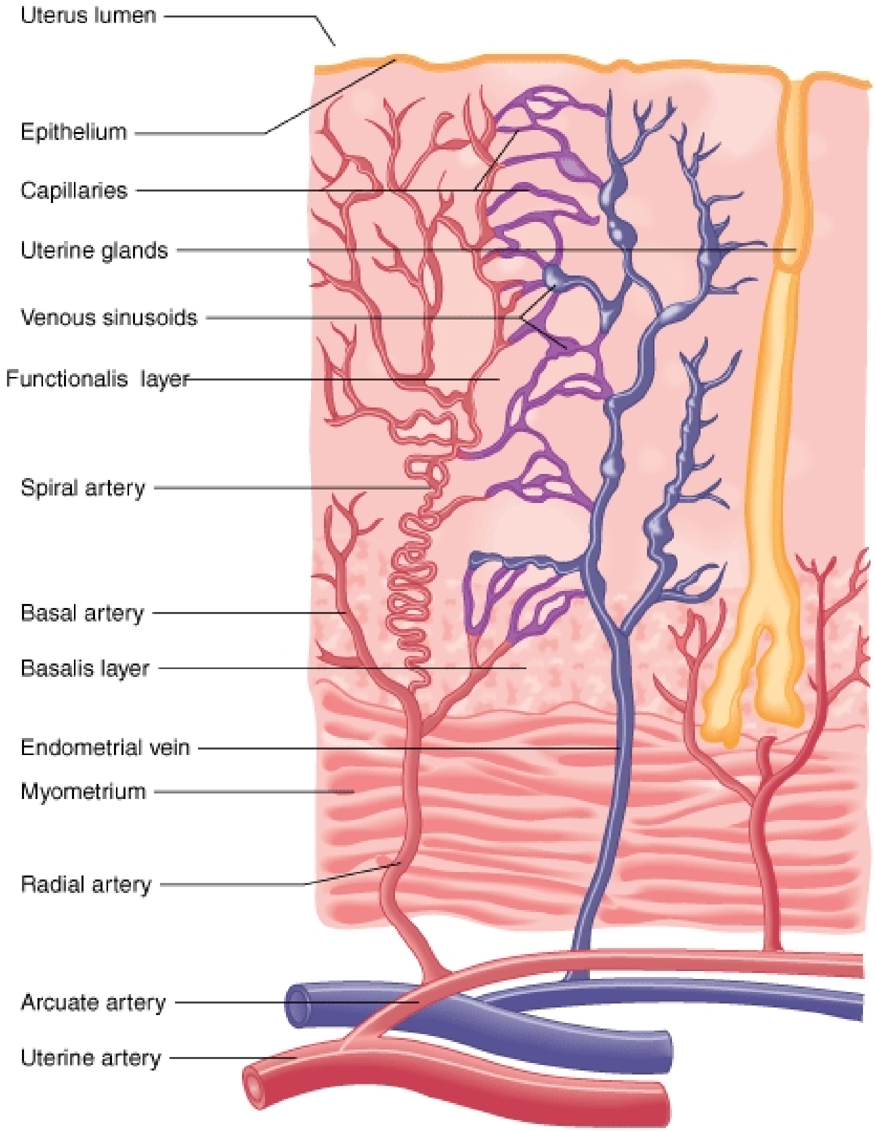
Even so, malignant neoplasms, especially endometrial carcinoma, are found more frequently in this age group than in others. Less commonly, estrogen-producing ovarian carcinoma may cause endometrial hyperplasia with uterine bleeding. Similarly, ulcerative vulvar, vaginal, or cervical neoplasms may also be sources. And rarely, egress of serosanguineous discharge from fallopian tube cancers can appear as uterine bleeding.

As with prepubertal females, because bleeding from the rectum, vagina, or urethra may be confused by an elderly woman. Thus, clear determination of the site of bleeding is critical.

PATHOPHYSIOLOGY

The endometrium consists of two distinct zones, the functionalis layer and the basalis layer (Fig. 8-2). The basalis layer stretches beneath the functionalis, lies in direct contact with the myometrium, and is less hormonally responsive. The basalis serves as a reservoir for the regeneration of the functionalis following menses. In contrast, the functionalis layer lines the uterine cavity, undergoes dramatic change throughout the menstrual cycle, and ultimately sloughs during menstruation. Histologically, the functionalis has a surface epithelium and underlying subepithelial capillary plexus. Beneath these are organized stroma and glands in which leukocyte populations are interspersed.

FIGURE 8-2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Endometrial vasculature.

Blood reaches the uterus via the uterine and ovarian arteries (Fig. 38-13). From these, the arcuate arteries are formed and supply the myometrium. These in turn branch into the radial arteries, which extend toward the endometrium at right angles from the arcuate arteries (see Fig. 8-2). At the endometrium-myometrium junction, the radial arteries bifurcate to create the basal and spiral arteries. The basal arteries serve the basalis layer of the endometrium and are relatively insensitive to hormonal changes

(Abberton, 1999; Hickey, 2000b; Weston, 2000). The spiral arteries stretch to supply the functionalis layer. Their arteriole branches are thought to be critical in controlling menstruation. Prior to menses these arterioles display increased coiling with stasis of blood flow. Subsequently, vasodilatation and bleeding from the spiral arteriole and capillary walls ensues. As a result, most menstrual blood is lost through these vessels. This is followed by vasoconstriction which leads to endometrial ischemia and necrosis. This necrotic tissue is sloughed with menstruation.

SYMPTOMS

Disturbance of the endometrial degeneration and sloughing in a regular cyclic fashion results in aberrant uterine bleeding. A number of clinical manifestations can develop.

Menorrhagia and Metrorrhagia

These are defined in Definitions and describe abnormalities of bleeding patterns, duration, and flow. Most pathologic disorders, however, do not consistently display specific patterns and may cause menorrhagia or metrorrhagia or both. As a result, in many cases the bleeding pattern in a particular woman is of limited value in diagnosing the underlying cause of bleeding, but can be used to assess improvement with treatment.

Postcoital Bleeding

Bleeding following intercourse most commonly develops in women aged 20 to 40 years and in those who are multiparous. No underlying pathology is identified in up to two thirds (Rosenthal, 2001; Selo-Ojeme, 2004). If an identifiable lesion is found, however, it typically is benign (Shalini, 1998). In a review of 248 women with postcoital bleeding, Selo-Ojeme and co-workers (2004) found that a fourth of cases were caused by cervical eversion (see Chap. 29, Cervix). Other causes included endocervical polyps, cervicitis, and less commonly, endometrial polyps. In the cases of cervicitis, *Chlamydia trachomatis* is a frequent cause. Bax and associates (2002) found that the relative risk of chlamydial infection in women with postcoital bleeding was 2.6 times higher than that of a control group without bleeding.

In some women, postcoital bleeding may be from cervical or other genital tract neoplasia. The epithelium associated with cervical intraepithelial neoplasia (CIN) and invasive cancer is thin and friable and readily detaches from the cervix. In women with postcoital bleeding, CIN was found in 7 to 10 percent, invasive cancer in about 5 percent, and vaginal or endometrial cancer in <1 percent (Rosenthal, 2001; Selo-Ojeme, 2004; Shalini, 1998). In another study, Jha and Sabharwal (2002) reported that a number of women with postcoital bleeding had pathologic lesions identified at colposcopic evaluation that had been missed by Pap smear screening. Thus, most women with unexplained postcoital bleeding should undergo colposcopic examination if no other obvious source of bleeding is identified.

Pelvic Pain

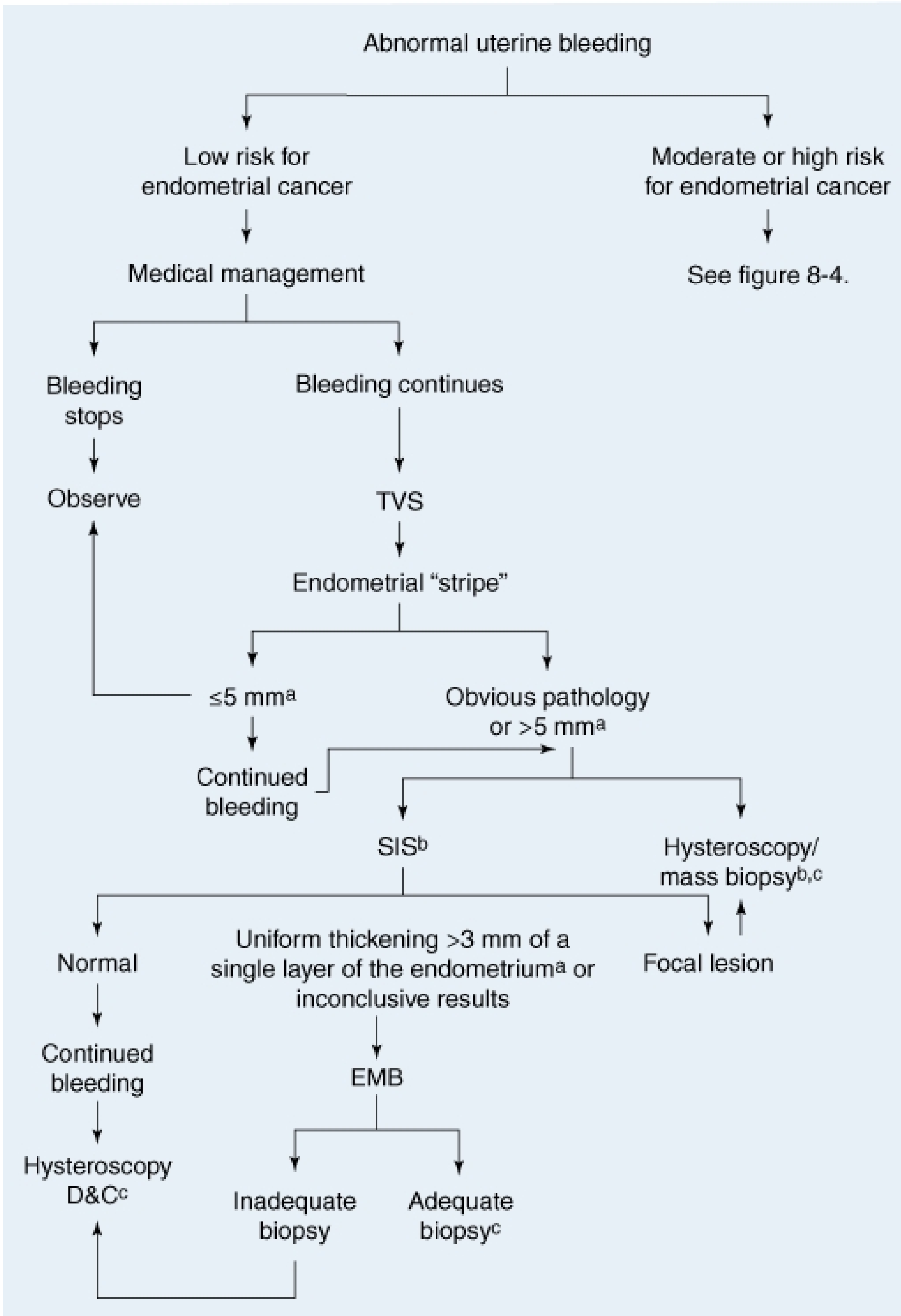
Because of the role of prostaglandins in both menorrhagia and dysmenorrhea, it seems logical that painful cramping would commonly accompany abnormal bleeding (Bieglmayer, 1995; Ylikorkala, 1994). And indeed, dysmenorrhea frequently develops concurrently with abnormal bleeding caused by leiomyomas polyps, adenomyosis, infections, and pregnancy complications.

Painful intercourse and noncyclic pain are less frequent in women with abnormal bleeding and usually suggests a structural or infectious cause. For example, Lippman and colleagues (2003) reported increased rates of dyspareunia and noncyclic pelvic pain in women with uterine leiomyomas. Similarly, Sammour and co-workers (2002) correlated increasing pelvic pain with deepening myometrial invasion with adenomyosis (see Chap. 9, Adenomyosis).

DIAGNOSIS

The diagnostic goal with abnormal uterine bleeding is to exclude cancer and to identify the underlying pathology to allow optimal treatment. Technologic advances have changed the evaluation of women with abnormal uterine bleeding, and sonography, endometrial biopsy, and hysteroscopy are used primarily. Many diagnostic algorithms of uterine bleeding focus on identification of endometrial cancer (Figs. 8-3 and 8-4). Eighty to 90 percent of women with this cancer present with abnormal bleeding.

FIGURE 8-3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

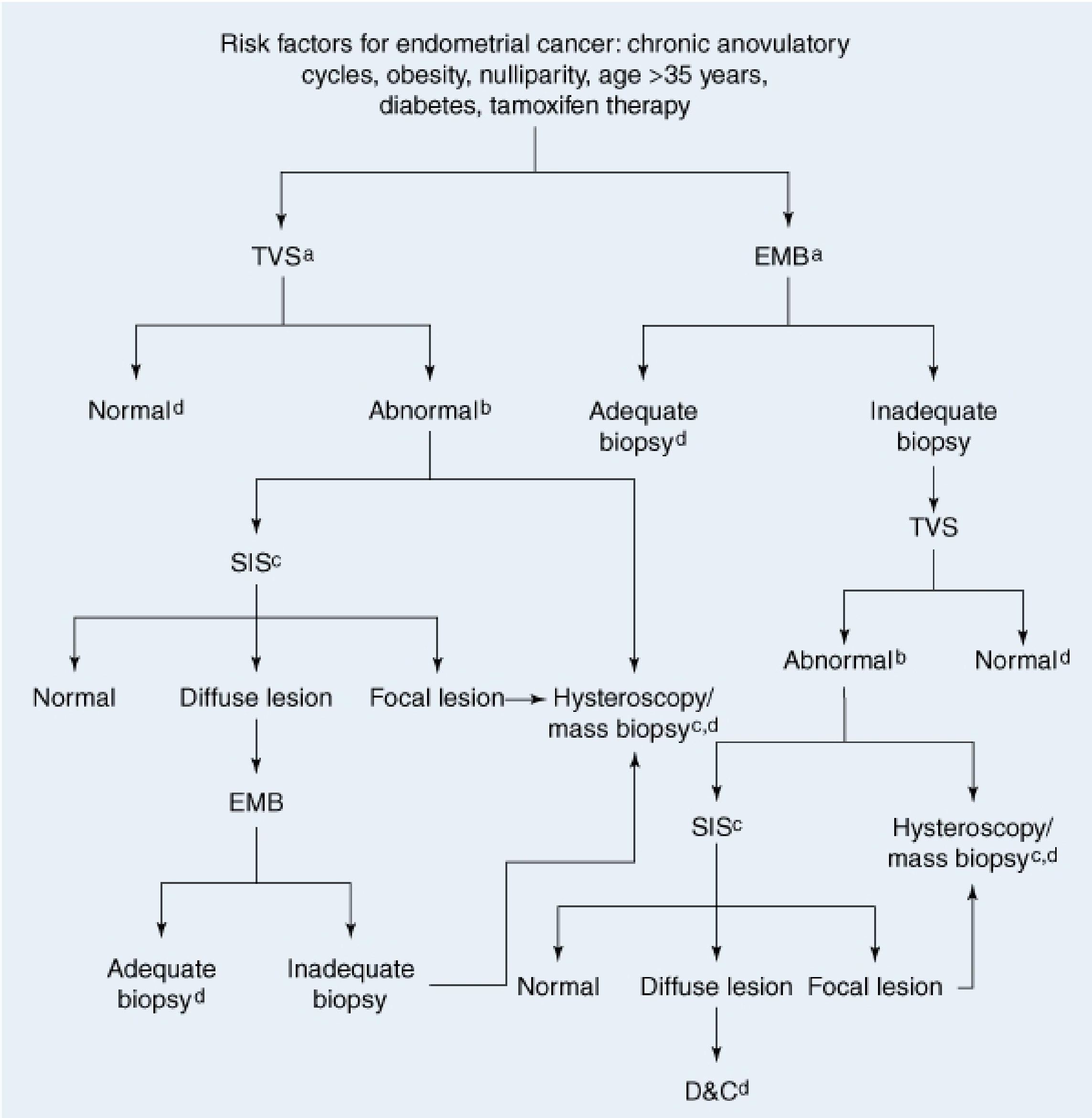
Diagnostic algorithm to identify endometrial pathology in patients with abnormal uterine bleeding. D&C = dilatation and curettage; EMB = endometrial biopsy; SIS = saline-infusion sonography; TVS = transvaginal sonography.

[a] Endometrium bilayer thickness measurements are used for postmenopausal women.

[b] SIS or hysteroscopy per physician preference.

c Adequate diagnosis and clinical management should follow.

FIGURE 8-4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Diagnostic algorithm to identify endometrial pathology in patients with abnormal uterine bleeding and with risk factors for endometrial cancer.

D&C = dilatation and curettage; EMB = endometrial biopsy; SIS = saline-infusion sonography; TVS = transvaginal sonography.

a TVS or EMB per physician preference.

b Endometrium bilayer >5 mm (in postmenopausal women) or obvious pathology seen.

c SIS or hysteroscopy per physician preference.

d Adequate diagnosis and clinical management should follow.

The incidence and risk of endometrial carcinoma increases with age and three fourths of women with this malignancy are postmenopausal. Thus, in postmenopausal patients, the need to exclude cancer intensifies and endometrial biopsy is warranted. In the remaining 25 percent of premenopausal women with endometrial cancer, only 5 percent are less than 40 years of age (Peterson, 1968). Most of these premenopausal women are obese or have chronic anovulation, or both (Rose, 1996). Thus, obese or anovulatory women with abnormal bleeding should also have endometrial cancer excluded. The American College of Obstetricians and Gynecologists (2000) recommends endometrial assessment in any woman older than 35 years with abnormal bleeding and in those younger than 35 years who are suspected of having anovulatory uterine bleeding refractory to medical management.

Clinical Evaluation

Initially, the site of uterine bleeding must be confirmed because bleeding may also come from the lower reproductive tract, gastrointestinal system, or urinary tract. This is more difficult when there is no active bleeding. In these situations, urinalysis or stool guaiac evaluation may be helpful adjuncts to a thorough examination.

Laboratory Evaluation

HEMATOLOGIC AND β-HCG TESTING

A hemogram is useful to evaluate anemia from chronic blood loss as well as the degree of blood loss in women with menorrhagia. An abnormally low serum ferritin level is a satisfactory predictor of blood loss >80 mL per menstrual cycle (Warner, 2004).

Pregnancy complications are quickly excluded with determination of urine or serum levels of human chorionic gonadotropin (β-hCG). Miscarriages and ectopic pregnancies may cause simple spotting or lead to life-threatening hemorrhage.

Screening for coagulation disorders should be considered in women with menorrhagia and no other obvious causes. This is particularly true for adolescents with menorrhagia. Evaluation typically includes partial thromboplastin time, prothrombin time, bleeding time, platelet count, and may include special testing for von Willebrand disease (von Willebrand Disease).

INFECTIONS

As discussed, cervicitis commonly causes intermenstrual or postcoital spotting (Lindner, 1988). In turn, the association between mucopurulent cervicitis and cervical infection with *Chlamydia trachomatis* and *Neisseria gonorrhoeae* is well established (see Chap. 3, Neisseria gonorrhoeae) (Marrazzo, 2002). The Centers for Disease Control and Prevention (2006) recommends testing for both when mucopurulent cervicitis is present. Cervicitis secondary to herpes simplex virus (HSV) infection may also cause bleeding (Paavonen, 1988).

CYTOLOGIC EXAMINATION

Both cervical and endometrial cancers can cause abnormal bleeding and evidence for these tumors can often be found with Pap smear screening.

The most frequent abnormal cytologic results involve squamous cell pathology and may reflect cervicitis, intraepithelial neoplasia, or cancer. Less commonly, atypical glandular or endometrial cells may be found. Any of these may suggest the cause of bleeding, and depending on the cytologic results, colposcopy or endometrial biopsy or both may be indicated (see Chap. 29, Colposcopy).

ENDOMETRIAL BIOPSY

Sampling and histologic evaluation of the endometrium in women with abnormal bleeding may disclose infection or neoplastic lesions such as endometrial hyperplasia, cancer, polyps, or gestational trophoblastic neoplasia (Table 8-2).

Table 8-2 Pertinent Findings in Endometrium in Women with Abnormal Bleeding According to Age									
	Age								
	Premenopausal <40 years(n = 460)			**Perimenopausal 40â€"55 years(n = 748)**			**Postmenopausal >55 years(n = 226)**		
Finding in Endometrial Specimen	**No.**	**%**		**No.**	**%**		**No.**	**%**	
Carcinoma	0	â€"		3	0.4		15	7	
Atypical hyperplasia	0	â€"		5	0.7		NK		
Hyperplasia	6	1		41	6		34	15	
Atrophy	7	2		51	7		127	56	
Polyp	6	1		13	2		19	8	
Proliferative	139	29		273	36		31	14	
Secretory	241	50		287	38		0	â€"	

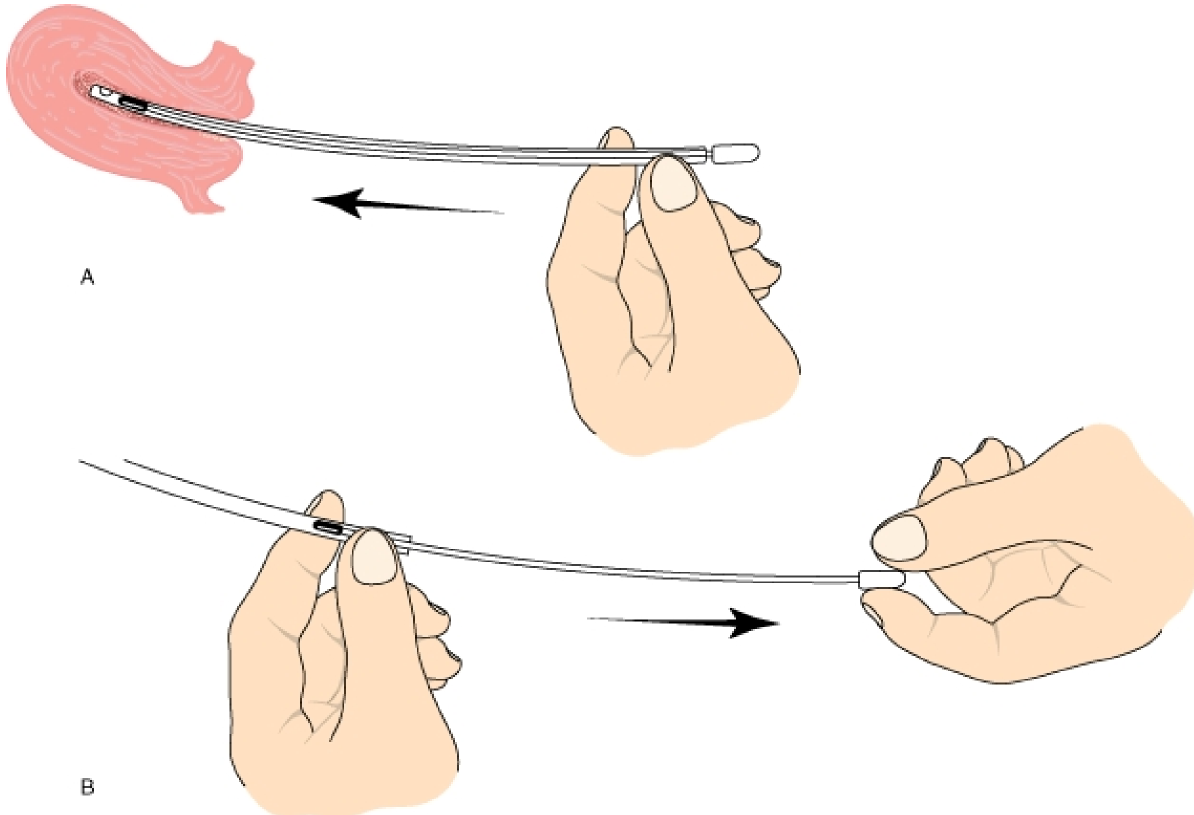
NK = not known.

From Ronnett, 2002, with permission.

For years, dilatation and curettage (D&C) was used for endometrial tissue sampling (see Section 41-16, Sharp Dilatation and Curettage). But because of the associated surgical risks, expense, postoperative pain, and need for operative anesthesia, other suitable substitutes were evaluated. In addition, several investigators have demonstrated high rates of incomplete sampling and missed pathology with D&C (Goldstein, 1997; Grimes, 1982; Stock, 1975).

Of suitable substitutes for D&C, office techniques using metal curettes were implemented to obtain endometrial samples, and these showed significant positive correlations with histologic results from hysterectomy specimens (Ferenczy, 1979; Stovall, 1989). The main disadvantages, however, were patient discomfort, cost, and procedural complications such as uterine perforation and infection. To minimize these, a variety of thin, flexible plastic samplers have been evaluated, with comparable histologic findings from tissues obtained by D&C, hysterectomy, or stiff metal curette (Stovall, 1991). In their meta-analysis of endometrial biopsy tools, Dijkhuizen and co-workers (2000) found the Pipelle (CooperSurgical, Trumbull, CT) to be superior (Fig. 8-5).

FIGURE 8-5



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

During biopsy, the Pipelle is first directed to the uterine fundus (**A**). The stylette of the Pipelle is retracted to create suction within the cylinder. (**B**). The Pipelle is then drawn to the internal cervical os and advanced back to the fundus. The Pipelle is gently spun during its advancement and retraction to allow thorough sampling of all endometrial surfaces. *(From Nichols, 1993, with permission.)*

Despite its advantages, there are limitations to endometrial sampling with the Pipelle device. First, a tissue sample that is inadequate for histologic evaluation or an inability to pass the catheter into the endometrial cavity is encountered in up to 28 percent of biopsy attempts (Smith-Bindman, 1998). Cervical stenosis is the most common cause of obstruction. An incomplete evaluation necessitates further investigation with D&C, transvaginal sonography, or diagnostic hysteroscopy (Emanuel, 1995). Second, endometrial biopsy has a cancer-detection failure rate of 0.9 percent. Thus, a positive histologic result is accurate to diagnose cancer, whereas a negative result does not necessarily exclude it. Therefore, if an endometrial biopsy with normal tissue is obtained, but abnormal bleeding continues despite conservative treatment or if the suspicion of endometrial cancer is high, then further diagnostic efforts are warranted (Clark, 2002; Hatasaka, 2005). Finally, endometrial sampling is associated with a greater percentage of false-negative results if the pathology is focal, such as with endometrial polyps. Guido and associates (1995) reported false-negative results in 11 of 65 patientsâ€”17 percentâ€”undergoing Pipelle endometrial sampling for abnormal bleeding. Five of these 11 had malignant tissue present only in endometrial polyps, and another three patients had disease localized to less than 5 percent of the endometrial surface. Because of these limitations with endometrial sampling, investigators have evaluated the use of sonography, hysteroscopy, or both to replace or complement endometrial sampling.

Sonography

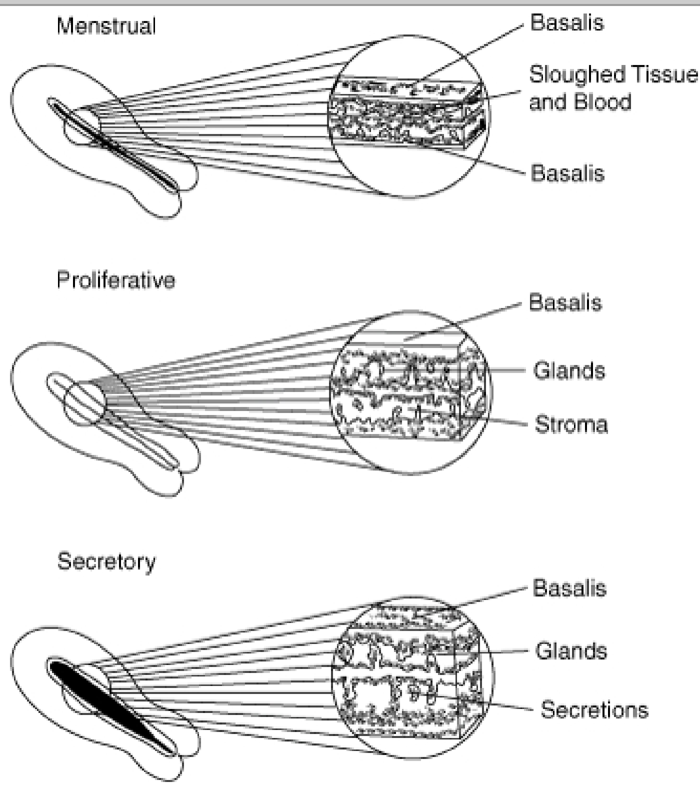
TRANSVAGINAL SONOGRAPHY

With its improved resolution, this technology is chosen by many instead of endometrial biopsy as a first-line tool to assess

abnormal bleeding. If abnormal bleeding stems from myometrial pathology such as leiomyomas or adenomyosis, sonography offers anatomic information regarding the myometrium that is not afforded by hysteroscopy or endometrial biopsy. In addition, transvaginal sonography (TVS) compared with these other two offers greater patient comfort and comparable detection of endometrial hyperplasia and cancer.

Endometrial thickness, which changes with the menstrual cycle (Fig. 8-6), has been correlated with endometrial cancer risk in postmenopausal women. In longitudinal views, opposed endometrial surfaces appear as a hyperechoic *endometrial stripe* down the center of the uterine body (see Fig, 2-11).

FIGURE 8-6



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Variation of endometrial thickness with progression through the menstrual cycle. *(From Fleischer, 1986, with permission.)*

Although the thickness of the endometrium varies, ranges have been established. Granberg and co-workers (1991) found thickness measurements of 3.4 Â± 1.2 mm in postmenopausal women with an atrophic endometrium, 9.7 Â± 2.5 mm in those with endometrial hyperplasia, and 18.2 Â± 6.2 mm in those with endometrial cancer. Subsequently, a number of investigations have focused on endometrial thickness as it relates to the risk of hyperplasia and cancer in postmenopausal women. Sensitivities of 95 to 97 percent have been reported using a measurement of ≤4 mm for exclusion of endometrial cancer. This guideline can be employed whether or not a patient is taking hormone replacement therapy (Bakour, 1999; Karlsson, 1995; Tsuda, 1997). Women with endometrial thicknesses >5 mm warrant additional evaluation with saline-infusion sonography (SIS), hysteroscopy, or endometrial biopsy.

Endometrial thickness guidelines, however, have not been established for premenopausal women. Merz and colleagues (1996) found that the normal endometrial thickness in premenopausal women did not exceed 4 mm on day 4 of the menstrual cycle, nor did it measure over 8 mm by day 8. In their review, Farquar and co-workers (1999) suggested that a persistent finding of endometrial thickness, independent of cycle day, measuring ≥12 mm should prompt further evaluation in these women, especially

in those with risk factors for endometrial carcinoma (see Chap. 33). Risks include extended abnormal uterine bleeding, chronic anovulation, nulliparity, diabetes, obesity, hypertension, and tamoxifen use (Hatasaka, 2005).

Qualities other than endometrial thickness are also considered, and textural changes may indicate pathology. For example, punctate cystic areas within the endometrium may indicate a polyp. Conversely, hypoechoic masses that distort the endometrium and originate from the inner layer of myometrium most commonly are submucosal fibroids. Although there are no specific sonographic findings that are characteristic of endometrial cancer, some findings have been linked with greater frequency. For example, intermingled hypo- and hyperechoic areas within the endometrium may indicate malignancy. Endometrial cavity fluid collections and an irregular endometrial-myometrial junction have also been implicated. Thus, even with a normal endometrial stripe width, endometrial biopsy or hysteroscopy with biopsy should be performed to exclude malignancy when there is heterogeneous endometrial echogenicity or fluid collection (Dubinsky, 2004; Krissi, 1998; Sheikh, 2000).

Although the use of these criteria can safely reduce endometrial biopsies for many patients, others consider false-negative rates to be too high with this strategy for evaluating postmenopausal women. They advocate hysteroscopy with direct biopsy or D&C to evaluate postmenopausal bleeding (Litta, 2005; Tabor, 2002). In other patient populations, the 5-mm guideline may also be inappropriate. For example, van Doorn and co-workers (2004) reported decreased diagnostic accuracy in diabetic or obese women, and they recommend consideration of endometrial sampling.

A major limitation of TVS is the higher false-negative rate in diagnosing focal intrauterine pathology. This results in part from the physical inability of TVS to clearly assess the endometrium when there is concurrent uterine pathology such as leiomyomas or polyps. These women warrant either saline-infusion sonography or hysteroscopy for further evaluation.

SALINE-INFUSION SONOGRAPHY

This simple, minimally invasive, and effective sonographic procedure can be used to accurately evaluate the myometrium, endometrium, and endometrial cavity (see Chap. 2, Saline-Infusion Sonography). To perform SIS, a small catheter is threaded through the cervical os into the endometrial cavity. Through this catheter, sterile saline is infused, and the uterus is distended. Sonography is then performed using a traditional transvaginal technique.

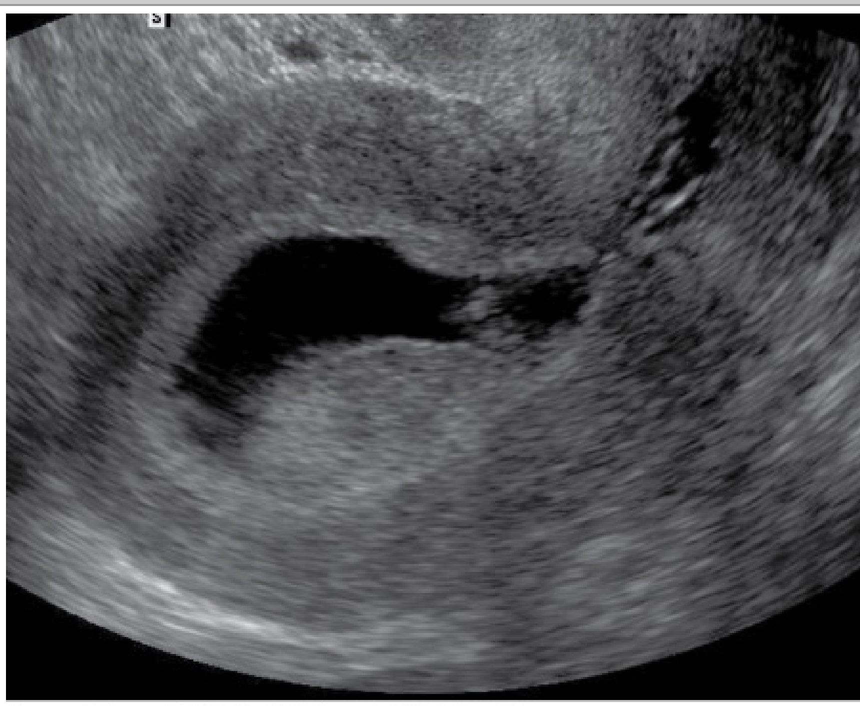
This method allows visualization of common masses associated with abnormal uterine bleeding such as endometrial polyps, submucosal myomas, and intracavitary blood clots. Whereas these frequently create nondescript distortion or thickening of the endometrial lining when imaged with TVS, SIS typically permits detection of intracavitary masses as well as differentiation of lesions as being endometrial, submucosal, or intramural (Figs. 8-7 and 8-8) (Pasrija, 2004; Ryu, 2004).

FIGURE 8-7

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Transvaginal sonography displays distortion and thickening of the endometrial stripe. *(Courtesy of Dr. Elysia Moschos.)*

FIGURE 8-8



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Saline-infusion sonography further delineates the size and qualities of this endometrial mass. *(Courtesy of Dr. Elysia Moschos.)*

Saline-infusion sonography (SIS) has also been compared with hysteroscopy to detect uterine cavitary focal lesions. De Kroon and co-workers (2003) performed a meta-analysis of 24 studies and reported SIS to equal the diagnostic accuracy of hysteroscopy.

Importantly, neither hysteroscopy nor SIS can reliably discriminate between benign and malignant focal lesions. Thus, because of the malignant potential of many focal lesions, excision of most structural lesions, when identified, is recommended for those with risk factors. For this, operative hysteroscopy is typically used.

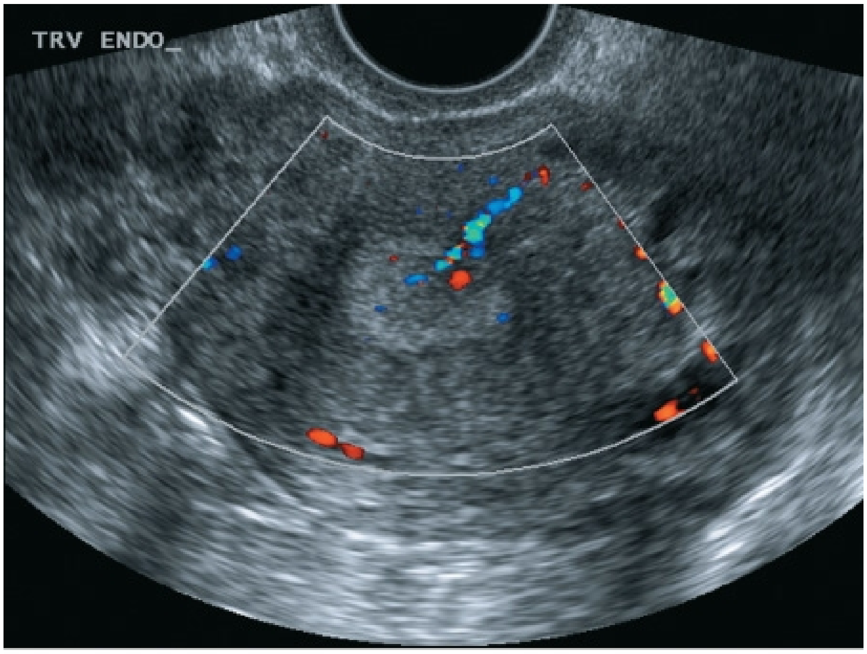
Another disadvantage to SIS is that it is best performed in the proliferative phase of the cycle to minimize false-negative and false-positive results. For example, focal lesions may be concealed in a thick, secretory endometrium. Also, the amount of endometrial tissue that can develop during the normal secretory phase can be mistaken for small polyps or focal hyperplasia (Goldstein, 2004). For many, SIS has more patient discomfort than TVS, and about 5 percent of examinations cannot be completed because of cervical stenosis or patient discomfort. As expected, stenosis is more prevalent in postmenopausal women (De Kroon, 2003). This rate of incompletion mirrors that of diagnostic hysteroscopy.

Although accurate for identifying focal lesions, SIS may not add to the value of TVS alone to evaluate diffuse lesions such as hyperplasia and cancer. Therefore, in postmenopausal women with abnormal bleeding, and in whom the exclusion of cancer is more relevant than evaluating focal intracavitary lesions, use of SIS as an initial diagnostic tool may not have advantages over TVS alone.

TRANSVAGINAL COLOR DOPPLER SONOGRAPHY

This technique has been evaluated in identifying and differentiating endometrial pathology in the context of uterine bleeding (Alcazar, 2003, 2004; Jakab, 2005). In one study, Fleischer and colleagues (2003) used transvaginal color Doppler sonography (TV-CDS) to differentiate between submucous leiomyomas and endometrial polyps. They reported that endometrial polyps had only one arterial supply, whereas submucosal leiomyomas generally received blood flow from several vessels arising from the inner myometrium (Fig. 8-9). Others have tried unsuccessfully to measure flow impedance to determine malignant transformation within polyps. Thus, hysteroscopic excision and histopathologic evaluation of endometrial polyps are still necessary for those at risk (Endometrial Polyp) (Goldstein, 2002).

FIGURE 8-9



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Transvaginal color Doppler sonography of an endometrial polyp. Color flow feature identifies a single feeder vessel, which is characteristic of polyps. *(Courtesy of Dr. Elysia Moschos.)*

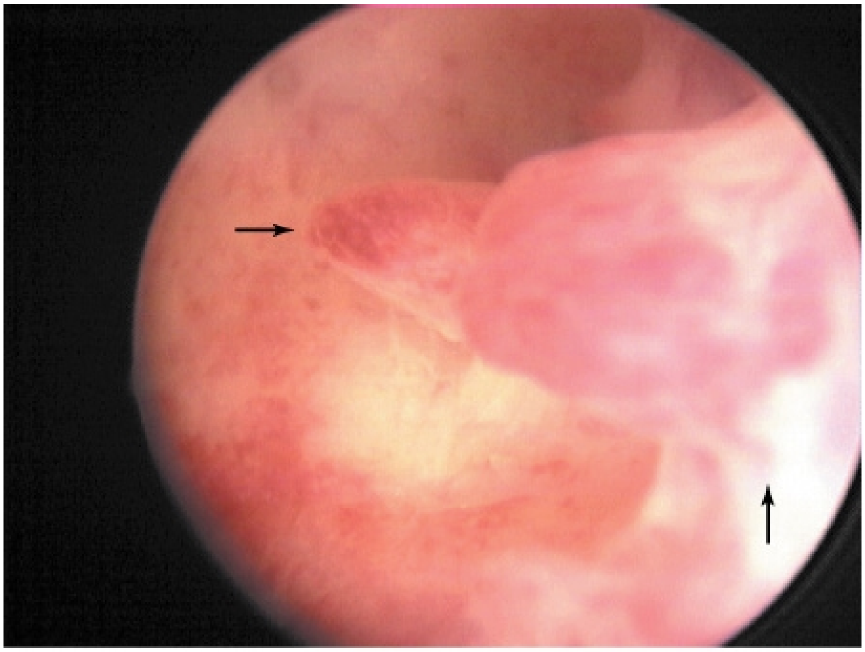
Three-dimensional sonography has been evaluated recently, but its contribution to the evaluation of abnormal uterine bleeding is also yet undefined (see Chap. 2, Three-Dimensional Sonography) (Clark, 2004; Makris, 2007).

Hysteroscopy

This procedure involves inserting an optic endoscope, usually 3 to 5 mm in diameter, into the endometrial cavity (see Section 41-35, Hysteroscopy). The uterine cavity is then distended with saline or another medium for visualization. In addition to inspection, biopsy of the endometrium allows histologic diagnosis of visually abnormal areas and has been shown to be a safe and accurate means to identify pathology (van Dongen, 2007). In fact, for many studies done to investigate the accuracy of TVS or SIS for evaluation of intracavitary uterine pathology, hysteroscopy is used as the gold standard for comparison.

The main advantage of hysteroscopy is to detect intracavitary lesions such as leiomyomas and polyps that might be missed using transvaginal sonography or endometrial sampling (Fig. 8-10) (Tahir, 1999). In fact, some have advocated hysteroscopy as the primary tool for the diagnosis of abnormal uterine bleeding. Although it is highly accurate for identifying endometrial cancer, it is less accurate for endometrial hyperplasia. Thus, some recommend endometrial biopsy or endometrial curettage in conjunction with hysteroscopy (Ben Yehuda, 1998; Clark, 2002).

FIGURE 8-10



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Hysteroscopy demonstrating an endometrial polyp. **Horizontal arrow** indicates polyp tip and the *vertical arrow* points to the polyp's base. *(Courtesy of Dr. Kevin Doody.)*

There are other limitations to hysteroscopy. Cervical stenosis sometimes will block successful introduction of the endoscope, and heavy bleeding may limit an adequate examination (Beukenholdt, 2003). The use of misoprostol, 100 mg orally the evening before and the morning of hysteroscopy, is useful for cervical softening in patients with suspected cervical stenosis. Hysteroscopy is more expensive and technically challenging than TVS or SIS. Many perform hysteroscopy in their office, whereas others prefer a day-surgery setting to provide increased patient analgesia. Obviously, greater cost and anesthetic risks can attend completion in this latter setting. Although it can be painful, use of a 3.5-mm minihysteroscope instead of the conventional 5-mm endoscope significantly decreases patient discomfort during office hysteroscopy (Cicinelli, 2003). Associated infection and uterine perforation have been reported with hysteroscopy, but fortunately their incidence is low (Bradley, 2002; Vercellini, 1997).

There is concern that peritoneal seeding with malignant cells may take place during hysteroscopy in some women subsequently diagnosed with endometrial cancer (Obermair, 2000; Zerbe, 2000). Caution is advised with hysteroscopy in women at high risk for endometrial cancer, and some suggest a negative endometrial biopsy result is necessary before hysteroscopy is done (Oehler, 2003). Although there may be a risk of peritoneal contamination by cancer cells with hysteroscopy, there is no evidence that the prognosis for patients is worsened (Revel, 2004).

Summary of Diagnostic Procedures

There is no one clear sequence to use of endometrial biopsy, TVS, SIS, and hysteroscopy when evaluating abnormal uterine bleeding. None of these will distinguish all anatomic lesions with high sensitivity and specificity. That said, TVS for several reasons is a logical first step. It is well-tolerated, cost-effective, and requires relatively minimal technical skill. Additionally, it has the advantage of reliably determining whether a lesion is diffuse or focal. Once anatomic lesions have been identified, subsequent evaluation requires individualization. If endometrial hyperplasia or cancer is suspected, then endometrial biopsy may offer advantages. Alternatively, possible focal lesions may be best investigated with either hysteroscopy or SIS. Ultimately, the selection of appropriate tests depends on their accuracy to characterize the most likely anatomic lesions.

DIFFERENTIAL DIAGNOSIS

Uterine bleeding may result from hormonal changes, complications of pregnancy, coagulopathies, infection, or neoplasia. The risks and incidences of these etiologies change significantly with age and reproductive status. In approximately one half of cases, no organic pathology is identified, and dysfunctional uterine bleeding is diagnosed, that is, a diagnosis of exclusion (Rees, 1987).

External Sources

INTRAUTERINE DEVICE

Copper-Containing Intrauterine Device

These intrauterine devices (IUDs) have long been associated with menorrhagia and metrorrhagia (see Chap. 5, Menorrhagia) (Milsom, 1995; Bilian, 2002). Several explanations for this bleeding have been suggested. At the cellular level, unbalanced ratios of prostaglandins and thromboxane have been proposed as a potential source of IUD-induced menorrhagia (Zhang, 1992). This gains credence in that clinical studies have shown improvement of menorrhagia with prostaglandin inhibitors such as nonsteroidal anti-inflammatory drugs (NSAIDs) (Roy, 1981).

At the tissue level, there is increased endometrial vascularity, congestion, and degeneration in IUD users. These changes result in interstitial hemorrhage which may lead to metrorrhagia (Shaw, 1979). In another study, Pan and co-workers (1995) found more severe degenerative changes in spiral arteriolar walls with marked dilatation of lumens in women with menorrhagia and who were using an IUD. They also identified a diminished local platelet count and less fibrin thrombus in this group and suggested that IUD-related bleeding might correlate with poor spiral arteriolar contraction and inadequate thrombus formation.

At the organ level some have suggested IUD rotation, embedding, or perforation may cause excessive bleeding. There have been studies that support as well as refute this (Faundes, 1997; Pizarro, 1989).

Initially, patients with IUD-related bleeding may be managed with empiric trials of NSAIDs (Table 8-3). Persistent abnormal bleeding, however, may result from other gynecologic pathology and not from the IUD. These patients should be managed similarly to other women with the complaint of abnormal uterine bleeding. Although sonographic evaluation may be limited by IUD shadowing, endometrial biopsy with small catheters can be performed without removal of the device (Grimes, 2004).

Table 8-3 Medical Treatment of Menorrhagia[a]

NSAID		
Mefenamic acid	500 mg tid for 5 days, beginning with menses	Bonnar, 1996
Naproxen	550 mg on first day of menses, then 275 mg daily	Hall, 1987
Ibuprofen	600 mg daily throughout menses	Makarainen, 1986a
Flurbiprofen	100 mg bid for 5 days, beginning with menses	Andersch, 1988
Meclofenamate	100 mg tid for 3 days, beginning with menses	Vargyas, 1987
Other classes		
COCs Tranexamic acid Norethindrone	One orally daily 1 g qid for 5 days, beginning with menses 5 mg tid days 5 through 26 of cycle (ovulatory DUB). 5 mg tid days 15 through 26 of cycle (anovulatory DUB)	Agarwal, 2001 Bonnar, 1996 Irvine, 1998 Higham, 1993
Danazol	100 mg or 200 mg daily throughout cycle	Chimbira, 1980b

GnRH agonists	3.75 mg intramuscularly each month (maximum 6 months of use)	Shamonki, 2000
LNG-IUS	Intrauterine placement	Reid, 2005

[a] All agents are administered orally except GnRH agonists and LNG-IUS.

bid = twice daily; COCs = combination oral contraceptive pills; DUB = dysfunctional uterine bleeding; GnRH = gonadotropin-releasing hormone; LNG-IUS = levonorgestrel-containing intrauterine system; NSAID = nonsteroidal anti-inflammatory drug; qid = four times daily; tid = twice daily

Data from Lethaby, 1998a, 1998b, 2000, 2004, 2005 and Beaumont, 2002, with permission.

Levonorgestrel-Containing Intrauterine System

This system, marketed as Mirena (Berlex, Wayne, NJ) (see Fig. 5-5), can lead to abnormal uterine bleeding in some users. The cause of bleeding is not clear, but downregulation of estrogen and progesterone receptors, increased local leukocyte populations, and alterations of endometrial vascular morphology, hemostasis, and endometrial repair have all been proposed (Oliveira-Ribeiro, 2004; Rhoton-Vlasak, 2005).

The endometrial effects of progestins are thought to predominate, and there is increasing evidence that low-dose progestins increase endometrial vascular fragility (Hickey, 2000a, 2002; Roopa, 2003). The LNG-IUS is associated with development of superficial, thin-walled vessels with increased diameters, that combined with irregularity of the endometrial surface, may cause the breakthrough bleeding commonly associated with its use. As the endometrium becomes atrophic, these vascular abnormalities gradually resolve at a time thought to coincide clinically with progestin-induced amenorrhea (McGavigan, 2003).

Bleeding associated with the LNG-IUS may be managed similarly to that with the copper-containing IUD, and NSAIDs serve as first-line treatment. Refractory cases warranted further evaluation for IUD displacement or intracavity pathology (Ronnerdag, 2007).

PROGESTIN-ONLY CONTRACEPTION

Bleeding disturbances are common not only with the LNG-IUS as described above, but also with other progestin-only methods of birth control. This bleeding is characteristically irregular and light, but may also be frequent and prolonged.

COMBINATION HORMONAL CONTRACEPTION

Bleeding associated with combination oral contraceptive pills (COCs) is common (see Chap. 5, Estrogen Plus Progestin Contraceptives). As many as 30 to 50 percent of women experience abnormal uterine bleeding in the first month that they use combination COCs (Hatcher, 2004). The presumed source of this bleeding stems from endometrial atrophy, which is induced by the progestin component of COCs. During this process, spiral arterioles do not characteristically coil, and they become thinner and more sinusoidal. In addition, venules become dilatated and prone to thrombosis. This often leads to local tissue infarction and is thought to be the cause of breakthrough bleeding (Deligdisch, 2000; Ober, 1977).

Fortunately, the incidence of bleeding decreases significantly with time. For example, Rosenburg and Long (1992) found that after 6 months of COC use, only approximately 10 percent of patients experienced breakthrough bleeding. Accordingly, during the early months of pill use, only counseling and reassurance are required (Schrager, 2002).

HORMONE REPLACEMENT THERAPY

Irregular spotting or bleeding is a well-known side effect of hormone replacement therapy (HRT) and is a common reason for discontinuation of treatment (see Chap. 22, Summary of Risks and Benefits) (Reynolds, 2002). Bleeding may develop both in women using continuous (daily) therapy and in those taking cyclic (sequential) replacement, but is less likely during the first year in those using a cyclic pattern (Lethaby, 2004).

TAMOXIFEN

This selective estrogen receptor modulator (SERM) is used as an adjunct for treatment of estrogen-receptorâ€"positive breast cancer. Although it diminishes estrogen action in breast tissue, its effects on the endometrium stimulate proliferation (see Chap.

12, Breast Cancer Prevention). Tamoxifen use has been linked to endometrial hyperplasia, polyps, and carcinoma as well as uterine sarcomas (Cohen, 2004).

Screening women who use tamoxifen and do not have abnormal bleeding has not proved effective. Protocols using sonography or endometrial biopsy failed to effectively identify endometrial cancer in asymptomatic users (Barakat, 2000; Love, 1999). As a result, women using tamoxifen should undergo evaluation for endometrial cancer only when bleeding develops.

Dysfunctional Uterine Bleeding

Once organic causes of abnormal uterine bleeding have been excluded, the term *dysfunctional uterine bleeding* (DUB) is used. Up to one-half of women with abnormal bleeding will have DUB (Hickey, 2000b). In 80 to 90 percent of these, bleeding results from dysfunction of the hypothalamic-pituitary-ovarian axis, which leads to anovulation (see Chap. 16). Because anovulatory cycles produce no progesterone to stabilize cyclic withdrawal of the estrogen-prepared endometrium, bleeding episodes become irregular and amenorrhea, metrorrhagia, and menorrhagia are common. For example, many women with anovulation may have amenorrhea for weeks to months followed by irregular, prolonged, and heavy bleeding.

In the other 10 to 20 percent of women with DUB, ovulation occurs cyclically, and menorrhagia is thought to originate from defects in the control mechanisms of menstruation.

PATHOPHYSIOLOGY

Anovulatory DUB

No progesterone is produced when ovulation does not occur, and thus proliferative endometrium persists. At the tissue level, presistent proliferative endometrium is often associated with stromal breakdown, decreased spiral arteriole density, and increased dilated and unstable venous capillaries (Singh, 2005). At the cellular level, the availability of arachidonic acid is reduced, and prostaglandin production is impaired. For these reasons, bleeding associated with anovulation is thought to result from changes in endometrial vascular structure and in prostaglandin concentration, and from an increased endometrial responsiveness to vasodilating prostaglandins (Hickey, 2000b, 2003).

Ovulatory DUB

Whereas anovulatory DUB results from alterations in vascular architecture and tone, ovulatory DUB is thought to stem predominantly from vascular dilatation alone. For example, women with ovulatory bleeding lose blood at rates three times faster than women with normal menses, but the number of spiral arterioles is not increased (Abberton, 1999). Thus in women with ovulatory DUB, it is thought that the vessels supplying the endometrium have decreased vascular tone and therefore increased rates of blood loss resulting from vasodilatation (Rogers, 2003). A number of causes that provoke this change in vascular tone have been suggested, and prostaglandins have been strongly implicated.

MEDICAL TREATMENT

Medical treatment of dysfunctional uterine bleeding includes tranexamic acid (antifibrinolytic agent), NSAIDs, COCs, progestins, androgens, and agonists of gonadotropin-releasing hormone (GnRH agonists) (see Table 9-3).

Nonsteroidal Anti-Inflammatory Drugs

These medicines are effective and well-tolerated oral agents commonly used for the treatment of DUB (see Table 8-3). The rationale for their use stems from the suspected role of prostaglandins in the pathogenesis of DUB. A number of investigators have documented the effectiveness of NSAIDs in decreasing DUB-related menorrhagia (Makarainen, 1986b; Marchini, 1995). Among NSAIDs, there are no differences in clinical efficacy, (Lethaby, 1998a).

Women lose 90 percent of menstrual blood volume during the first 3 days of menses (Haynes, 1977). Accordingly, NSAIDs are most effective if used with the onset of menses or just prior to its onset and continued throughout its duration. Therefore, one advantage to NSAIDs is that they are required only during menstruation. Another advantage is that commonly associated dysmenorrhea also improves with NSAIDs.

The so-called "conventional" NSAIDs nonspecifically inhibit both cyclooxygenase-1 (COX-1), an enzyme critical to normal platelet

function, and COX-2, which mediates inflammatory response mechanisms. They are effective analgesics, but their use with bleeding may not be ideal considering their inhibitory effects on platelet function. The other class of NSAIDs inhibits only COX-2 and does not interfere with platelet aggregation and hemostasis (Leese, 2000). Some have proposed that COX-2 inhibitors might be more effective to treat menorrhagia, however, there have been no randomized trials that validate this idea (Hayes, 2002). Additionally, there are now concerns that long-term use of COX-2 inhibitors is associated with increased myocardial infarction, stroke, and heart failure (Solomon, 2005). As a result, further investigation is needed before routine use of COX-2 inhibitors is recommended for menorrhagia.

Tranexamic Acid

This is an antifibrinolytic drug that exerts its effects by reversibly blocking lysine binding sites on plasminogen. The resulting decreased plasmin levels diminish fibrinolytic activity within endometrial vessels to prevent bleeding. The drug has no effect on other blood coagulation parameters such as platelet count, activated partial thromboplastin time, and prothrombin time (Wellington, 2003).

In women with DUB, there is increased fibrinolytic activity within the endometrium compared with women with normal menses (Gleeson, 1994). Clinically, the drug has been shown effective to reduce bleeding in up to half of women with DUB-related menorrhagia (Coulter, 1995; Lethaby, 2000). In addition, tranexamic acid requires administration only during menstruation and has few minor reported side effects. These are predominantly gastrointestinal and dose-dependent.

Tranexamic acid is approved for the treatment of DUB in Japan, the European Union, and Australia, as well as other countries, but not in the United States. It use has been limited by concern for complications from increased systemic thrombotic activity.

Etamsylate (Ethamsylate)

This hemostatic agent is the diethylammonium salt of dihydroxy-2,5 benzenesulphonate. It has been in clinical use for more than 30 years, but its mechanism of action is still not completely understood. Also spelled *ethamsylate,* this agent is suspected to act in early hemostasis by increasing platelet adhesiveness and aggregation (Hernandez, 2004). Its effectiveness varies in randomized trials and ranges from no reduction in flow to a 50 percent decrease (Bonnar, 1996; Chamberlain, 1991). Because of its inconsistent efficacy, in the United States, etamsylate does not have a clinical role in the treatment of menorrhagia (Irvine, 1999).

Oral Progestins

As discussed earlier, unopposed estrogen stimulation, resulting from anovulatory cycles, causes proliferation of the endometrium and erratic bleeding. Progestins halt endometrial growth and allow for an organized sloughing with their withdrawal (Saarikoski, 1990). Thus, progestin treatment of women with anovulatory DUB is usually successful. Of the oral progestins, either norethindroneâ€”also known as norethisteroneâ€”or medroxyprogesterone acetate may be used. For immediate control of bleeding, norethindrone, 5 mg, is given two or three times daily, or medroxyprogesterone acetate 10 mg is taken once daily for 10 days. This is followed by withdrawal bleeding 3 to 5 days after completion of the either course. For long-term management, similar dosages of these drugs are given during days 16 through 25 following commencement of the most recent menstrual flow (Fraser, 1990). Again, withdrawal bleeding will follow cessation each month.

In contrast, ovulatory menorrhagia is not due to a progestin deficiency but may result from altered prostaglandin synthesis or disruption of hemostasis. As expected, ovulatory menorrhagia is relatively unresponsive to cyclic administration of oral progestins (Cameron, 1987, 1990; Preston, 1995; Singh, 2005).

Despite this, women with ovulatory DUB may respond to longer treatment schedules. Norethindrone 5 mg or medroxyprogesterone acetate 10 mg, each given three times orally daily for days 5 to 26 of each menstrual cycle have been shown effective (Fraser, 1990; Irvine, 1998). Unfortunately, prolonged use of high-dose progestins is often associated with side effects such as mood changes, weight gain, bloating, headaches, and atherogenic changes in the lipid profile (Lethaby, 1998b). For these reasons, they are considered unacceptable by many women for long-term use.

Combination Oral Contraceptive Pills

Evidence suggests that these hormonal contraceptives are effective in the treatment of DUB, and when used long term, reduce flow

by 40 to 70 percent (Agarwal, 2001; Fraser, 1991). Advantages to COC use include the additional benefits of reducing dysmenorrhea and providing contraception (see Chap. 5, Estrogen Plus Progestin Contraceptives). Their presumed method of action is endometrial atrophy. There may also be diminished prostaglandin synthesis and decreased endometrial fibrinolysis (Irvine, 1999).

In addition to chronic use for the treatment of dysfunctional uterine bleeding, COCs can be used acutely to manage menorrhagia. Pills containing at least 30 μg of ethinyl estradiol should be prescribed. If there is active bleeding, the regimen begins with four pills every 6 hours until the bleeding has stopped for at least 24 hours. An antiemetic may be needed to control nausea. For most women, bleeding will cease within 48 hours. After the bleeding has stopped, the dosage of COC is decreased to three pills per day for the next 3 days, followed by two pills per day for 3 days. A once-a-day regimen is then continued for 21 days to be followed by withdrawal menses. At this point, COCs may be stopped or continued for cycle control (Rimsza, 2002). Alternatively, less frequent dosing or smaller doses may also be effective in the acute management of menorrhagia.

Estrogen

High-dose estrogen therapy may be useful in controlling acute bleeding episodes because it promotes rapid endometrial growth to cover denuded surfaces. Conjugated equine estrogens (Premarin, Wyeth Pharmaceuticals, Madison, NJ) are administered orally at dosages up to 10 mg daily given in four divided doses. Similarly, the drug can be given intravenously in 25-mg doses every 4 hours for up to three doses (DeVore, 1982). Once bleeding has slowed, patients can be transitioned to an oral taper using COCs.

Androgens (Danazol and Gestrinone)

Danazol is an isoxazole derivative of the synthetic steroid 17α-ethinyl testosterone (see Chap, 10, Androgens). The net effect of danazol creates a hypoestrogenic and hyperandrogenic environment, which induces endometrial atrophy. As a result, menstrual loss is reduced by approximately half, and it may even induce amenorrhea in some women (Beaumont, 2002; Chimbira, 1980a; Higham, 1993).

For heavy menstrual bleeding, suggested dosing is 100 to 200 mg taken orally every day (Chimbira, 1980b). Unfortunately, this agent has significant androgenic side effects that include weight gain, oily skin, and acne. It is thus usually reserved as a second-line drug for short-term use prior to surgery (Bongers, 2004).

Gestrinone is derived synthetically from a 19-nortestosterone steroid nucleus. Its mechanism of action, side effects, and indications for the treatment of menorrhagia are similar to danazol. The recommended dose for the treatment of menorrhagia is 2.5 mg daily every 3 to 4 days. The drug is used in the United Kingdom and other countries, but is not approved for use in the United States.

Gonadotropin-Releasing Hormone Agonists

The profound hypoestrogenic state created by these agents induces endometrial atrophy and amenorrhea in most women (see Chap. 9, GnRH Agonists). Side effects, however, may be dramatic and include those typical for the menopause (see Chap. 21, Hypothalamus-Pituitary-Ovarian Axis Changes). In addition, associated bone loss precludes their long-term use. This family of drugs, however, may be helpful for short-term use in inducing amenorrhea and allowing women to rebuild their red blood cell mass prior to surgery.

Levonorgestrel-Containing Intrauterine System

Intrauterine devices were developed for contraceptive purposes, but the levonorgestrel-containing intrauterine system (LNG-IUS) also provides relief of menorrhagia for some women (see Chap. 5, Levonorgestrel-Containing Intrauterine Device).

The addition of progestins to inert intrauterine devices was found to decrease expulsion, improve contraceptive action, and in some cases, improve menorrhagia (Barrington, 1997). The LNG-IUS device was designed to take advantage of these attributes, and it has been shown to reduce menstrual loss by 74 to 97 percent after 3 months use (Singh, 2005; Stewart, 2001). The LNG-IUS can be used in all women as a first line of treatment of menorrhagia in place of oral medications. It is particularly useful for reproductive-aged women who also desire contraception.

SURGERY

For many women, conservative medical management may either be unsuccessful or associated with significant side effects. For

women whose symptoms are poorly managed with medical options, surgical management of menorrhagia may include procedures to destroy the endometrium and hysterectomy.

Dilatation and Curettage (D&C)

Curettage is rarely used for long-term treatment because its effects are only temporary. In the occasional woman, D&C is performed to arrest severe bleeding refractory to high-dose estrogen administration (American College of Obstetricians and Gynecologists, 2000; Stabinsky and associates 1999). An illustrated description of D&C is found in Section 41-16, Sharp Dilatation and Curettage.

Endometrial Destructive Procedures

Although medical therapy is generally used first, over half of women with menorrhagia undergo hysterectomy within 5 years of referral to a gynecologist. In at least a third of these, an anatomically normal uterus is removed (Coulter, 1991; Roy, 2004). As alternatives to hysterectomy, less invasive procedures have been devised that either destroy or resect the endometrium and lead to amenorrhea in a manner similar to Asherman syndrome (see Section 41-36, Endometrial Ablation Procedures).

It is problematic that endometrial tissue has tremendous regenerative capabilities. For this reason, to be successful, destructive procedures must remove the endometrial functionalis and basalis as well as 3 mm of myometrial depth. However, the persistence or regeneration of endometrium is possible. Therefore, premenopausal women should be counseled before surgery about the need for adequate postoperative contraception.

In addition, the American College of Obstetricians and Gynecologists (2007) recommends endometrial sampling prior to surgery. Women with endometrial hyperplasia or cancer should not undergo ablation.

Currently acceptable procedures for endometrial resection or ablation use laser, radiofrequency, electrical, or thermal energies (Oehler, 2003). They are described as either first- or second-generation techniques according to their temporal introduction into use and their need for hysteroscopic guidance. A number of studies that compare first- and second-generation techniques have shown them equally effective (Gervaise, 1999; Meyer, 1998).

Both first- and second-generation procedures require dilation of the cervix to admit the ablative device. They are typically performed using general anesthesia or conduction analgesia. However, some have described the use of paracervical block and/or intravenous sedation for second-generation procedures (Fernandez, 1997; Soysal, 2001; Wallage, 2003). Recently, Marsh and co-workers (2005) described the use of thermal balloon ablation using only preoperative ibuprofen.

There are three first-generation methods. Two of these, the neodymium:yttrium-aluminum-garnet (Nd-YAG) laser and rollerball destroy the endometrium. In contrast, the third method, transcervical resection of the endometrium (TCRE), surgically removes it. All three require advanced operative hysteroscopic skills and a fluid distention medium. Complications from excess systemic absorption of these media can be severe and are discussed in Section 41-35, Hysteroscopy.

Table 8-4 Second-Generation Endometrial Ablation Technologies
• Hot liquid balloons
ThermaChoice I, II, and III
Cavaterm and Cavaterm plus
Thermablate
• Hydrothermablation
• Cryoablation (Her option)
• Microwave endometrial ablation
• Impedance controlled ablation (NovaSure)

Table 8-5. Absolute Contraindications for Endometrial Ablation

- Genital tract malignancy
- Women wishing to preserve their fertility
- Pregnancy
- Expectation of amenorrhea
- Acute pelvic infection
- Prior uterine surgeryâ€"classical cesarean delivery, transmural myomectomy.

Adapted from Vilos, 2004, with permission.

After resection or ablation, 70 to 80 percent of women experience significantly decreased bleeding, and 15 to 35 percent of these develop amenorrhea. Increasing treatment failures due to endometrial regeneration accrue with time following the procedure. For example, in a long-term surveillance of 301 women following ablation, Martyn and co-workers (1998) reported that the cumulative failure rate increased from 13 percent at 2 years to 27 percent at 5 years. Long-term surveillance of women following ablation shows an approximate 20 percent ultimate hysterectomy rate (Aberdeen Endometrial Ablation Trials Group, 1999; Furst, 2007).

Although success rates for treatment of heavy bleeding are not as high as with hysterectomy, patient satisfaction rates are surprisingly comparable. Moreover, resection and ablation procedures have significantly lower complication rates when compared with hysterectomy.

Hysterectomy

Removal of the uterus is obviously the most effective treatment for bleeding and overall patient satisfaction rates approximate 85 percent. Moreover, subjective improvement of dysmenorrhea and premenstrual symptoms has also been reported following hysterectomy (Aberdeen Endometrial Ablation Trials Group, 1999; Mousa, 2001). Disadvantages to hysterectomy include more frequent and severe intraoperative and postoperative complications compared with either conservative medical or ablation procedures. Operating time, hospitalization, recovery times, and costs are also greater. The procedure is discussed in detail in Section 41-19, Hysterectomy.

Structural Abnormalities

PATHOLOGY ASSOCIATED WITH UTERINE ENLARGEMENT

Structural abnormalities are common causes of abnormal bleeding, and of these, leiomyomas by far are the most common. The impact of these tumors in clinical gynecology cannot be overstated. Less frequent structural causes of bleeding include adenomyosis, hematometra, and hypertrophic myometrium. A detailed discussion of these disorders and their treatment is presented in Chapter 9, Uterus.

MÃ¼LLERIAN DEFECTS

Congenital structural lesions of the reproductive tract may at times cause chronic intermenstrual bleeding superimposed upon normal menstrual cycles (see Chap. 18, Description and Patient Presentation). In such cases, an anomalous partial vaginal septum may collect blood behind it. Although sequestered, a small patent outflow from the collection typically allows chronic release. Patients thus describe cyclic menses with light but persistent intermenstrual flow.

ARTERIOVENOUS MALFORMATION

A uterine arteriovenous malformation (AVM) is a mixture of arterial, venous, and small capillary-like channels with fistulous connections. They may be congenital or acquired. The size of the vessels varies considerably and they may be large and tortuous or much smaller and uniform (Majmudar, 1998). Acquired AVMs are usually single, large vessels that result from trauma at cesarean delivery or D&C, from cervical or endometrial cancer, from gestational trophoblastic disease, or from IUD use (Ghosh, 1986). Uterine AVMs are rare. They more commonly involve the corpus, but are also found in the cervix (Lowenstein, 2004).

Affected patients commonly present with menorrhagia or menometrorrhagia soon after a miscarriage, uterine surgery, or curettage. Heavy uterine bleeding without associated cervical trauma or uterine perforation may be presenting signs. Additionally, uterine atony that fails to respond to conventional therapies should raise suspicion for this abnormality following delivery (Chang, 2004). Symptoms can appear slowly or suddenly and with life-threatening bleeding (Timmerman, 2003).

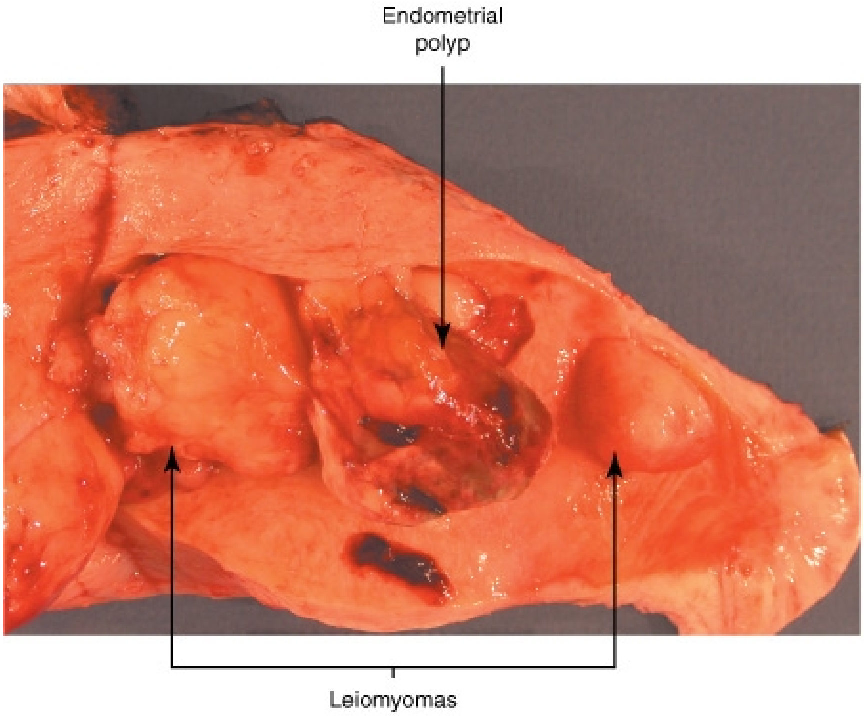
In some cases, AVMs are first visualized with sonography because of its ready availability and widespread use. Sonographic characteristics are nonspecific and may include hypoechogenic tubular structures within the myometrium. Color Doppler sonography may provide a more specific image with thickened vessels and blood flow reversals. Angiography is used to confirm the diagnosis of AVMs, although computed-tomography (CT) scanning with contrast, magnetic resonance (MR) imaging saline-infusion sonography, and hysteroscopy have also been described (Lowenstein, 2004; Timmerman, 2003).

Arteriovenous malformations have been treated traditionally by hysterectomy. A number of investigators, however, have demonstrated the effectiveness of arterial embolization of feeder vessels (Halperin, 2007; Majmudar, 1998).

ENDOMETRIAL POLYP

These soft, fleshy intrauterine overgrowths are comprised of endometrial glands and fibrotic stroma and are covered by a surface epithelium (Fig. 8-10 and 8-11). Polyps are common, and their prevalence ranges from 10 to 30 percent in women with abnormal bleeding (Bakour, 2000; Goldstein, 1997). As shown in Figure 8-11, intact polyps may be single or multiple, may measure from a few millimeters to several centimeters, and may be sessile or pedunculated with a long and slender stalk (Kim, 2004). Most polyps are benign, but hyperplasia develops frequently. Moreover, malignant transformation develops in 1 to 2 percent of polyps (Ben Arie, 2004; Machtinger, 2005; Savelli, 2003).

FIGURE 8-11



Endometrial polyp found within the endometrial cavity of a hysterectomy specimen. Note the complicated appearance of this cavity with submucous leiomyomas and endometrial polyp. *(Courtesy of Dr. Raheela Ashfaq.)*

Several factors have been implicated in the growth of endometrial polyps. Gene translocations involving chromosomes 6 and 12 have been linked with polyp development (Vanni, 1993; Dal Cin, 1992). Some studies implicate estrogen and progesterone as important mediators because they cause endometrial glands, stromal tissue, and spiral arteries to elongate, which gives the characteristic polypoid appearance to these growths (Jakab, 2005).

The few risk factors associated with development of endometrial polyps include hypertension and obesity as well as tamoxifen use (Reslova, 1999). Most evidence does not support a link between hormone replacement therapy and polyp formation (Bakour, 2002; Lahti, 1993; Maia, 2004).

More than 70 percent of women with endometrial polyps will complain of menorrhagia or metrorrhagia (Preutthipan, 2005; Reslova, 1999). It is thought that stromal congestion within the polyp leads to venous stasis with apical necrosis and bleeding (Jakab, 2005). Although bleeding is common, with the introduction of transvaginal sonography, a large number of women with asymptomatic polyps have been identified during imaging for other indications (Goldstein, 2002).

Infertility has been indirectly linked to some endometrial pathology. Small studies have shown increased pregnancy rates and fewer early pregnancy losses in infertile women following hysteroscopic excision (Preutthipan, 2005; Shokeir, 2004; Varasteh, 1999). Moreover, a randomized trial by Perez-Medina (2005) demonstrated a doubling of the pregnancy rate following intrauterine insemination (IUI) in infertile women following polypectomy compared with a group with polyps and infertillity managed with IUI alone. Although the exact mechanisms related to infertility are unknown, several causes have been suggested. Metalloproteinases associated with implantation and cytokines that impact embryo development have been implicated. Both are found in greater amount in polyps than normal surrounding uterine tissue (Inagaki, 2003). Alternatively, some investigators have found polyps in disproportionate numbers near the tubal ostia, and these may hinder ostium function and affect sperm migration (Shokeir, 2004;

Venturini, 1987). For these reasons, many advocate polyp removal in infertile women.

Although the risk of malignant transformation within polyps is low, it is more common with increasing age, hypertension, tamoxifen use, and polyp size greater than 1.5 cm. In some studies, malignant transformation has been reported only in postmenopausal patients (Anastasiadis, 2000; Cohen, 2004).

Transvaginal sonography, SIS, and hysteroscopy have evolved as the main diagnostic tools for evaluation of endometrial polyps. Although endometrial biopsy may identify polyps, it has decreased sensitivity for detecting focal lesions compared with these imaging modalities.

In premenopausal women with abnormal bleeding, TVS is best performed prior to day 10 of the cycle to lower the risk of false-positive findings. Using TVS, an endometrial polyp may appear as a nonspecific endometrial thickening or as round or elongated focal masses within the endometrial cavity (Fig. 8-7). Sonolucent cystic spaces corresponding to dilated endometrial glands may be seen within some polyps (Nalaboff, 2001).

Transvaginal sonography may be augmented with color Doppler. Visualization of a single feeding vessel is typical of endometrial polyps as shown in Figure 8-9 (Fleischer, 2003). Unfortunately, flow impedance measurements using color Doppler have failed to accurately determine the malignant potential of these lesions. Thus, excision and histopathologic evaluation of polyps are still necessary in those with risk factors (Goldstein, 2002).

Saline-infusion sonography (SIS) and hysteroscopy are both highly accurate in imaging endometrial polyps (see Figs. 8-8 and 8-10) (Nanda, 2002; Soares, 2000). Using SIS, polyps appear as echogenic, smooth, intracavitary masses with either broad bases or thin stalks and are outlined by fluid (Jorizzo, 2001). Hysteroscopy identifies nearly all cases of endometrial polyps (see Fig. 8-10). The main advantage of hysteroscopy is the ability to identify and often remove the polyp concurrently.

Whereas the Pap smear is not an effective tool to identify polyps, occasionally it incidentally leads to their identification. For example, 5 percent of postmenopausal women with benign endometrial cells identified on Pap smear were found to have endometrial polyps (Wu, 2001; Karim, 2002). Moreover, in those with atypical glandular cells, endometrial polyps were the most common underlying pathology found by investigators (Obenson, 2000).

Once a polyp has been identified, operative hysteroscopy is often the treatment of choice. The technique is detailed in Section 41-38, Polypectomy. Hysteroscopy and polypectomy is recommended for symptomatic women or for those with risk factors for malignant transformation (Savelli, 2003; Machtinger, 2005). Conversely, asymptomatic premenopausal women with polyps <1.5 cm can be observed. There is only a small associated risk of malignant transformation and high rates of spontaneous resolution (Ben Arie, 2004; DeWaay, 2002).

ENDOCERVICAL POLYP

These lesions represent overgrowths of benign endocervical stroma covered by epithelium. They appear as single, red, smooth elongated masses extending from the external os (see Fig. 4-13). Polyps vary in size and range from several millimeters to 2 or 3 cm. These common growths are found more frequently in multiparas and rarely in prepubertal females. Endocervical polyps are typically asymptomatic, but they can cause metrorrhagia, postcoital bleeding, and symptomatic vaginal discharge.

Endocervical polyps are usually identified by visual inspection during pelvic examination. In some instances, Pap smear findings of atypical glandular cells have been associated with endocervical polyps (Burja, 1999; Obenson, 2000). Although typically benign, malignant transformation may develop in 1 percent. Importantly, cervical cancer can present as polypoid masses and can mimic these benign lesions. For this reason, removal and histologic evaluation are recommended for an endocervical polyp.

Endocervical polyps are removed by grasping the polyp with a ring or polyp forceps. The polyp is twisted repeatedly about the base of its stalk to strangulate its feeding vessels. With repeated twisting the base will avulse. Monsel solution (ferric subsulfate) can be applied with direct pressure to the resulting stalk stub to complete hemostasis.

Infection

In addition to cervicitis, chronic endometritis can also lead to abnormal bleeding. Chronic endometritis was found by Greenwood and colleagues (1981) in 3 to 10 percent of endometrial biopsies performed for abnormal bleeding. Although bleeding is common

with chromic endometritis, women may also complain of vaginal discharge and lower abdominal pain. Chronic endometritis may develop insidiously, and usually follows abortion, pregnancy, and pelvic inflammatory disease (PID). As discussed further in Chapter 3, Diagnosis abnormal uterine bleeding may be observed in some women with acute as well as subclinical or silent PID (Ness, 2004; Wiesenfeld, 2002).

Diagnosis is made with endometrial biopsy. Women with biopsy-proven endometritis frequently have other lower genital tract infection concurrent with endometritis (Korn, 1995; Toth, 2007). In one study, Wiesenfeld and co-workers (2002) found subclinical PID and endometritis in 27 percent of women with Chlamydia trachomatis, in 26 percent of women infected with *Neisseria gonorrhoeae,* and in 15 percent of those with bacterial vaginosis. Antibiotic treatment comparable to that for PID usually results in cessation of bleeding symptoms (Eckert, 2004).

Pregnancy Associated

Abnormal bleeding during early pregnancy is encountered in 15 to 20 percent of pregnancies (Everett, 1997; Weiss, 2004). Although frequently no reason is found to account for bleeding, it may reflect early abortion, ectopic pregnancy, cervical infection, or polyp. A detailed discussion of bleeding associated with pregnancy is found in Chapters 6, Threatened Abortion and 7, Symptoms. The almost universal availability of sonography and β-hCG testing have revolutionized the assessment of bleeding in this setting.

Systemic Causes

RENAL DISEASE

Severe renal dysfunction is frequently accompanied by endocrine disturbances with amenorrhea, hypoestrogenism, and infertility (Matuszkiewicz-Rowinska, 2004). In a study of 100 women with chronic renal failure undergoing dialysis, Cochrane and Regan (1997) reported that 80 percent of those menstruating complained of menorrhagia. The mechanism behind these abnormalities is not clear, but hypothalamic dysregulation of gonadotropin secretion is suspected (Bry-Gauillard, 1999).

Treatment of abnormal bleeding due to chronic renal insufficiency is problematic. Prostaglandin synthase inhibitors are contraindicated because they cause renal artery vasoconstriction with adverse effects on glomerular function. Administration of cyclic progestins is typically unhelpful, and instead, Cochrane and Regan (1997) suggest high-dose medroxyprogesterone acetate to cause amenorrhea from endometrial atrophy. They also reported that most women with renal insufficiency respond to low-dose COCs, which offer the additional benefit of improved cycle control. However, in women with severe hypertension, these are typically contraindicated.

If women with severe menorrhagia cannot take or do not respond to medical therapy, then surgical treatments are considered. Jeong and co-workers (2004) found endometrial ablation to be successful, with 87 percent of women showing improvement of abnormal bleeding. In some women, however, hysterectomy is required.

LIVER DISEASE

Depending on its severity, liver dysfunction causes high rates of menstrual abnormalities (Stellon, 1986). In studies evaluating menstruation in women with end-stage liver disease before transplantation, menstrual dysfunction is reported in 60 percent (de Koning, 1990; Mass, 1996). The underlying mechanism for bleeding is not clear, but as in renal failure, hypothalamic-pituitary-ovarian (HPO) axis dysfunction has been implicated. The liver serves a primary role in the metabolism and excretion of sex hormones, and liver dysfunction is associated with high levels of circulating estrogen. In addition, there may be inappropriately low serum LH and FSH levels, indicating dysfunction of the HPO axis (Bell, 1995; Cundy, 1991).

Hemostatic dysfunction may also contribute to abnormal bleeding. With the exception of von Willebrand factor, all of the coagulation proteins and most of their inhibitors are synthesized in the liver. In addition, thrombocytopenia is common in women with portal hypertension and splenomegaly.

THYROID DISEASE

Both hyperthyroidism and hypothyroidism can cause menstrual disturbances ranging from amenorrhea to menorrhagia (Koutras, 1997). Although thyroid dysfunction can result in a spectrum of symptoms, in many women, menstrual abnormalities antedate

other clinical findings of thyroid disease (Joshi, 1993). Thus, in most women with abnormal uterine bleeding, serum thyroid-stimulating hormone (TSH) level measurement is recommended.

With hyperthyroidism, hypomenorrhea and amenorrhea are more frequent complaints. Menorrhagia is noted in only about 5 percent. Treatment of thyrotoxicosis improves menstrual regularity in most cases.

Women with severe overt hypothyroidism commonly present with anovulation, amenorrhea, and anovulatory DUB (Chap. 16, Hyperprolactinemia and Hypothyroidism). These women may also display defects in hemostasis. This may be due to decreased levels of several coagulation factors that have been identified in these women. Treatment of the underlying hypothyroidism usually corrects bleeding dysfunction (Krassas, 1999; Wilansky, 1989).

COAGULOPATHY

Whereas hemostatic defects are infrequent causes of gynecologic bleeding, in the subset of women with menorrhagia and normal anatomy, the incidence is significantly higher (Kadir, 1998; Philipp, 2005).

The American College of Obstetricians and Gynecologists (2001) recommends testing for bleeding disorders in: (1) adolescents with severe menorrhagia, (2) women with significant menorrhagia without another identifiable cause, and (3) preoperatively, prior to hysterectomy planned for severe bleeding. The initial screening evaluation of bleeding disorders in general has included a prothrombin time (PT), partial thromboplastin time (PTT), platelet count, and bleeding time. More commonly identified coagulopathies include von Willebrand disease (vWD) and other disorders of platelet function. Deficiencies of factor VII and IX (hemophilia A and B) or other factor deficiencies are more rarely involved.

Thrombocytopenia

Platelets are an integral part of thrombus formation. Their concentration in blood varies during the menstrual cycle, increasing following ovulation and falling at the onset of menses. In some women, clinically significant changes in platelet count or function can lead to abnormal bleeding.

von Willebrand Disease

Von Willebrand factor (vWF) is a large multimeric glycoprotein integral to hemostasis. It acts as an adhesive protein in clot formation at sites of vessel injury. It also prevents inactivation and clearance of factor VIII, which is depleted rapidly without vWF and becomes clinically deficient (Mendolicchio, 2005). There are several variants of the disease that are determined by the amount and function of vWF produced (Table 8-6).

Table 8-6 Phenotypic Classification and Genetic Transmission of von Willebrand Disease.

Phenotype	Mechanism of Disease	Genetic Transmission
1	Partial quantitative deficiency of von Willebrand factor (and factor VIII)	Autosomal dominant[a]
2	Qualitative defects of von Willebrand factor	Autosomal dominant[b]
3	Severe or complete deficiency of von Willebrand factor and moderately severe factor VIII deficiency	Autosomal recessive

[a] This mode of transmission is sometimes not evident because of reduced penetrance and varied expressivity.

[b] Rare cases are characterized by autosomal recessive transmission.

Adapted from Mannucci, 2004a, with permission.

Consideration of von Willebrand Disease (vWD) in young women is important because its prevalence is 1 to 2 percent in the general population (Rodeghiero, 1987). In women with abnormal bleeding and normal pelvic anatomy, rates of vWD were found to be 13 percent (Shankar, 2004). The disorder is more common in Caucasian than in African-American women (Miller, 2003).

Patients with vWD commonly complain of menorrhagia, and rates of 60 to 70 percent have been noted (Kadir, 1998, 1999; Lak, 2000). Heavy menstruation begins with menarche in these patients. Moreover, they commonly have other bleeding symptoms such as easy bruising, bleeding from the nose or gums, and postpartum or postoperative bleeding (Lee, 2005).

Testing for this bleeding disorder should be considered when evaluating women with menorrhagia for coagulopathies. Depending on the type and severity of vWD, the PTT and bleeding time may be prolonged. The American College of Obstetricians and Gynecologists (2001) recommends the ristocetin cofactor assay (vWF:RCo) to aid diagnosis. Importantly, vWF levels may be higher during the luteal phase, and thus samples should be obtained prior to day 7 of the menstrual cycle (Kadir, 1999; Lee, 2005). Consultation with a hematologist is recommended because diagnosis of vWD, especially in its mild form, is difficult.

Treatments for women with menorrhagia and vWD include desmopressin, plasma concentrates, hormonal contraception, antifibrinolytics, and surgery. Combination oral contraceptive pills have been noted to arrest uterine hemorrhage in 88 percent of women (Foster, 1995). Also, Kingman and co-workers (2004) reported that the LNG-IUS effectively decreased blood loss and induced amenorrhea in 56 percent of women with inherited bleeding disorders. Preliminary success has been found with endometrial ablation for women with vWD-related menorrhagia (El-Nashar, 2007; Rubin, 2004). Hysterectomy, of course, is curative and preoperative consultation with a hematologist is recommended.

For severe bleeding, replacement of vWF and factor VIII by plasma concentrates is given along with desmopressin. This vasopressin analog promotes release of vWF from storage sites in patients with the common type 1 vWD. The drug is available in an intravenous and a concentrated intranasal form (Lee, 2005).

Coagulation Factor Deficiencies

A number of these may result in menorrhagia. Deficiency of a procoagulant factor usually manifests as a prolonged prothrombin time or activated partial thromboplastin time.

Hemophilia A and B are inherited X-linked deficiencies of factor VIII or IX. Women carriers of the gene, however, can have decreased levels of factor VIII or IX. In some cases, these are low enough to cause mild hemophilia (Mannucci, 2001; Siegel, 2005).

Deficiencies of other coagulation factors are usually inherited as autosomal recessive traits and are rare. This group includes dysfibrinogenemia, hypofibrinogenemia, prothrombin deficiency, and deficiency of factors V, VII, X, XI, and XIII. Treatment of these disorders is by factor replacement (Mannucci, 2004b).

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PELVIC MASS: INTRODUCTION

Pelvic masses are common clinical findings and may involve the reproductive organs or nongynecologic structures. They may be identified in asymptomatic women during routine pelvic examination or may cause symptoms. Typical complaints include pain, pressure sensations, dysmenorrhea, or abnormal uterine bleeding. Although most pelvic masses are acquired lesions, a few arise as congenital anomalies. As a part of evaluation, laboratory tests are typically uninformative, but levels of serum β-human chorionic gonadotropin (β-hCG) or tumor markers may be helpful. Initially, imaging with sonography is preferred, but computed tomography (CT) or magnetic resonance (MR) imaging may be useful if the nature of the mass is still uncertain. Treatment of pelvic masses varies with patient symptoms, age, and risk factors. Although medical management is possible for many of these masses, for others, surgical treatment offers the highest success rates.

DEMOGRAPHIC FACTORS

Age has the greatest influence in evaluation of a pelvic mass. Pathology varies greatly with age, and neoplasms are more prevalent in older women.

Prepubertal Girls

The majority of gynecologic pelvic masses in this age group involve the ovary. Even during childhood, the ovaries are typically active, and many of these masses are functional cysts (de Silva, 2004; Deligeoroglou, 2004). Neoplastic lesions usually are benign germ cell tumors, and mature cystic teratomas (dermoid cysts) are the most common (Brown, 1993; Templeman, 2000). Malignant ovarian tumors in children and adolescents are rare and account for only 0.9 percent of all malignancies in this age group (see Chap. 36) (Young, 1975).

Adolescents

For the most part, the incidence and type of ovarian pathology found in adolescents is similar to those seen in prepubertal girls. With the onset of reproductive function, however, pelvic masses in adolescents may also include endometriomas and the sequelae of pelvic inflammatory disease and pregnancy. Gynecologic masses present a special diagnostic challenge in children and adolescents, because benign neoplasms greatly outnumber malignant ones, and their clinical signs and symptoms are often nonspecific. Multimodal techniques for diagnosis in these age groups are discussed in Chapter 14, Prepubertal Ovarian Cysts.

Reproductive-Aged Women

A number of genital tract disorders cause pelvic masses in adult women. Uterine enlargement due to pregnancy, functional ovarian cysts, and leiomyomas are among the most common. Endometrioma, mature cystic teratoma, acute or chronic tubo-ovarian abscess, and ectopic pregnancies are other frequent causes.

Postmenopausal Women

With the cessation of ovulation and reproductive function, the causes of pelvic mass also change. Simple ovarian cysts and leiomyomas are still a common source. Although atrophy of leiomyomas typically follows menopause, uterine enlargement can still be noted in many women. Importantly, malignancy is a more frequent cause of pelvic masses in this demographic group. Uterine tumors, including adenocarcinoma and sarcoma, have associated uterine enlargement. In addition, ovarian cancer accounts for nearly 4 percent of cancers among all women, with an estimate of over 25,000 new cases diagnosed annually in the United States (Barnholtz-Sloan, 2003).

UTERUS

Uterine enlargement is common and most frequently is the result of pregnancy or leiomyomas. Less often, enlargement is from adenomyosis, hematometra, or an adherent adnexal mass.

Leiomyomas

Leiomyomas are benign smooth muscle neoplasms that typically originate from the myometrium. They are often referred to as *uterine myomas,* and are incorrectly called *fibroids* because the considerable amount of collagen contained in many of them creates a fibrous consistency. Their incidence among women is generally cited as 20 to 25 percent, but has been shown to be as high as 70 to 80 percent in studies using histologic or sonographic examination (Buttram, 1981; Cramer, 1990; Day Baird, 2003).

In many women, leiomyomas are clinically insignificant. Conversely, in some, their number, size, or location within the uterus can provoke a myriad of symptoms. Taken together, symptoms caused by these uterine tumors constitute an important segment of gynecologic practice.

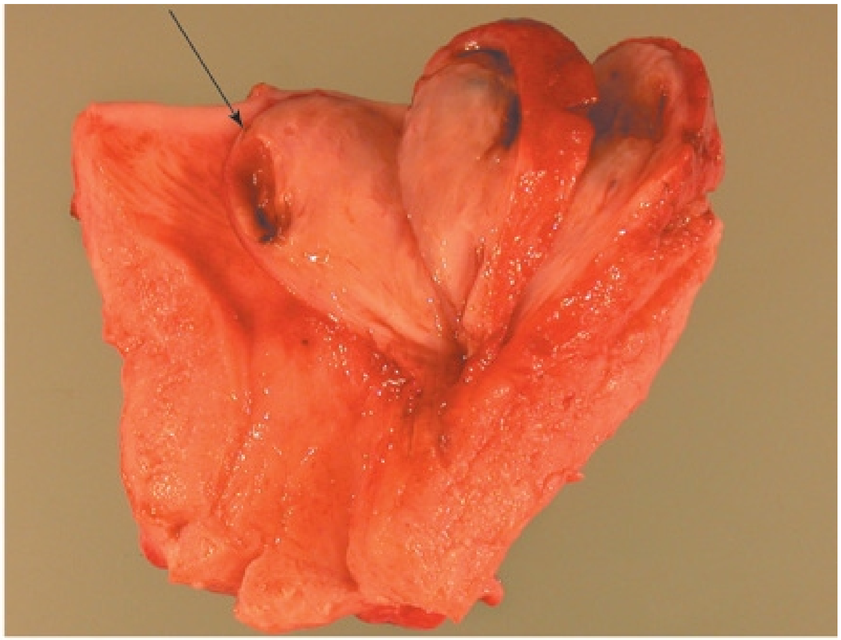
PATHOLOGIC APPEARANCE

Grossly leiomyomas are round, pearly white, firm, rubbery tumors that on cut-surface display a whorled pattern. A typically involved uterus contains 6 to 7 tumors of varying size (Cramer, 1990). Leiomyomas possess a distinct autonomy from their surrounding myometrium because of a thin outer connective tissue layer. This clinically important arrangement allows leiomyomas to be easily "shelled out" of the uterus during surgery.

Histologically, leiomyomas contain elongated smooth muscle cells aggregated in bundles that swirl and intersect at right angles to one another. Mitotic activity, however, is rare and is a key point in differentiation from leiomyosarcoma (see Chap. 34, Leiomyosarcoma) (Zaloudek, 2002).

The appearance of leiomyomas may vary when normal muscle tissue is replaced with various degenerative substances following hemorrhage and necrosis. This process is collectively termed *degeneration,* and these gross changes should be recognized as normal variants (Fig. 9-1). Degeneration develops frequently in leiomyomas because of the limited blood supply within these tumors. Leiomyomas have a lower arterial density compared with the surrounding normal myometrium (Fig. 9-2). Moreover, there is no intrinsic vascular organization and this disorganization leaves some tumors vulnerable to hypoperfusion and ischemia (Farrer-Brown, 1970; Forssman, 1976). Acute pain may accompany degeneration.

FIGURE 9-1



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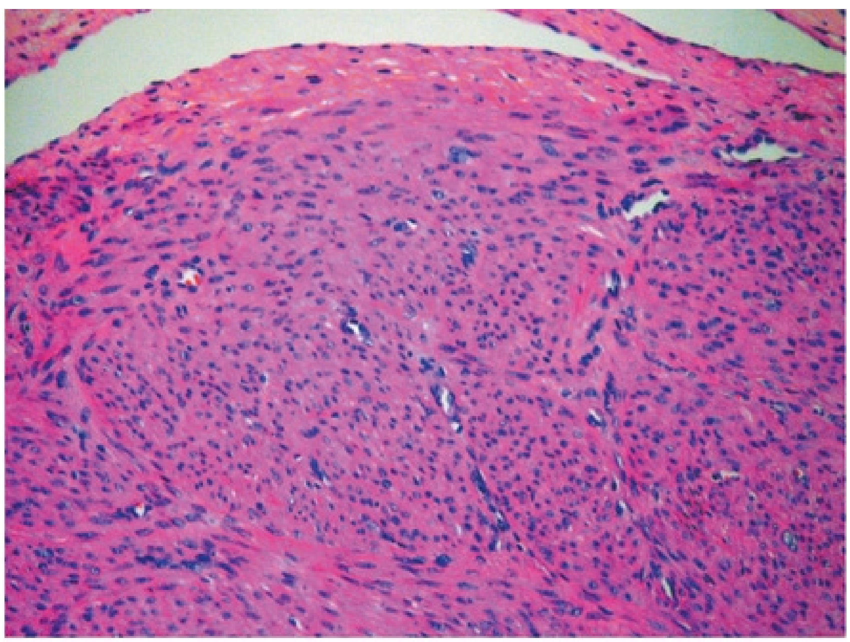

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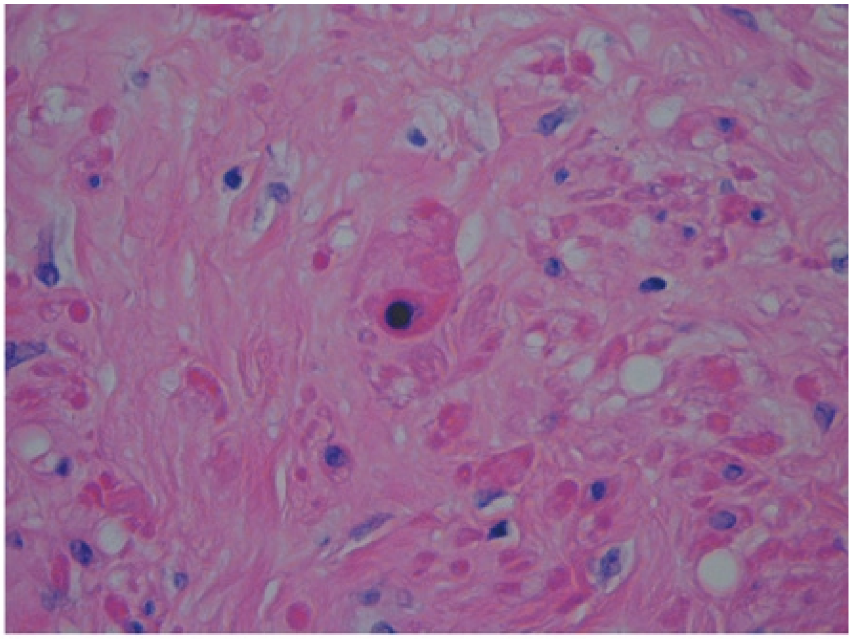
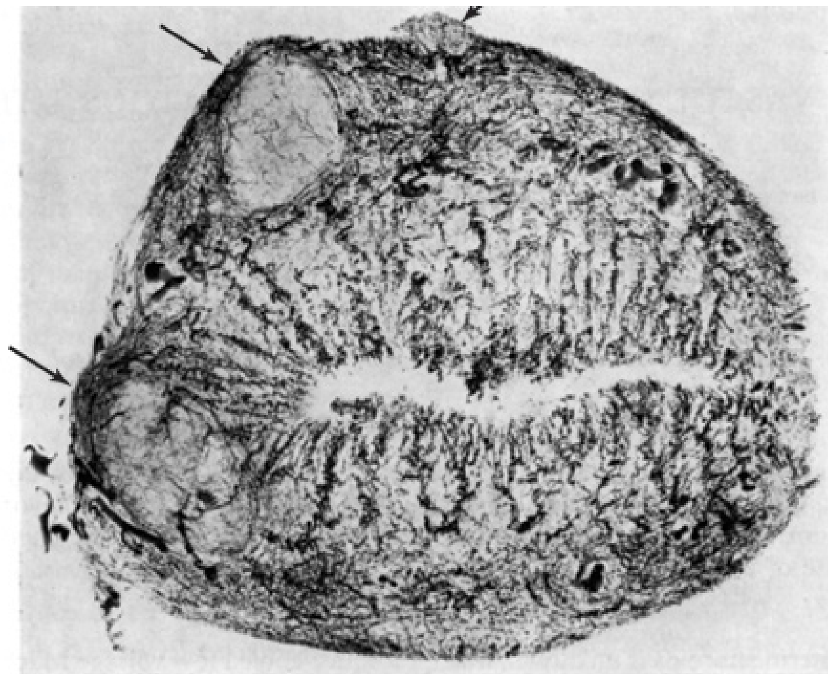


C

The appearance of leiomyomas will vary depending on the degree and type of degeneration present. **A.** Cystic degeneration (**arrow**) seen within this submucous fibroid. **B.** Typical histologic architecture of leiomyomas. **C.** Hyaline degeneration is identified by abundant pink glassy hyaline that is seen interspersed between smooth muscle cells. *(Courtesy of Dr. Raheela Ashfaq.)*

FIGURE 9-2



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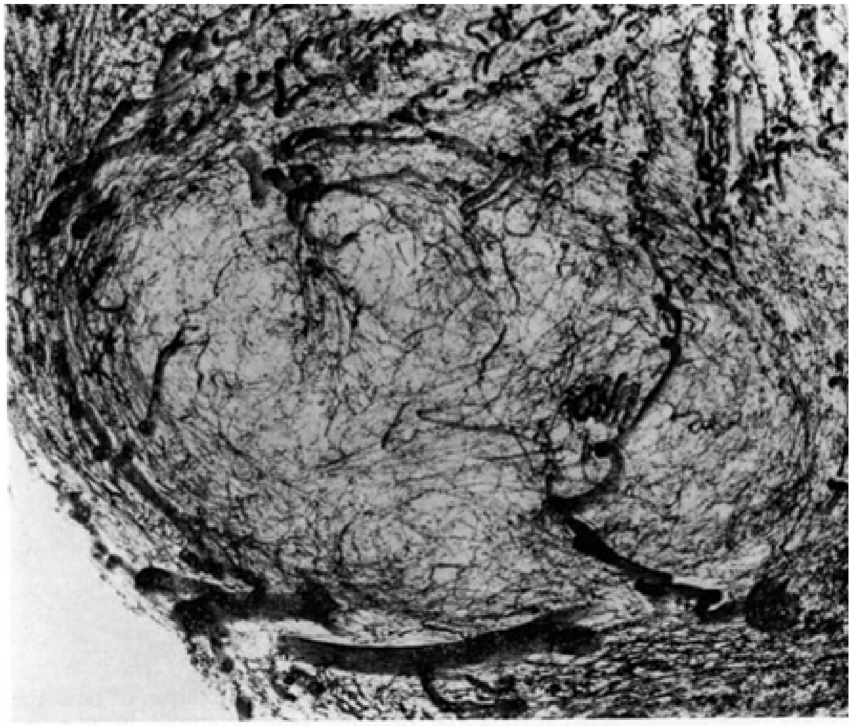


B

A. Transverse slice of uterus following arterial injection shows the diminished arterial supply in a subserosal and two intramural leiomyomas (**black arrows**). **B.** Higher magnification of the arterial supply in the lower of the two intramural leiomyomas. Note the poor vascular support of the inner portion of this leiomyoma. *(From Farrer-Brown, 1970, with permission.)*

CYTOGENETICS

Each leiomyoma is derived from a single progenitor myocyte. Thus, multiple tumors within the same uterus each show independent cytogenetic origins (Mashal, 1994; Townsend, 1970). The primary mutation initiating tumorigenesis is unknown, but identifiable karyotypic defects are found in about 40 percent of leiomyomas (Rein, 1998; Xing, 1997). A number of unique defects involving chromosomes 6, 7, 12, and 14 have been identified to correlate with rates and direction of tumor growth (Brosens, 1998). It is anticipated that further characterization of the specific functions of these karyotypic changes will help to define the important steps in leiomyoma development.

ROLE OF HORMONES

Estrogens

Uterine leiomyomas are estrogen- and progesterone-sensitive tumors (Table 9-1). Consequently, they develop during the reproductive years and regress in size and incidence after menopause. This concept is integral in understanding many of the risk factors associated with leiomyoma development and in formulating treatment plans. Sex steroid hormones likely mediate their effect by stimulating or inhibiting transcription and production of cellular growth factors.

Table 9-1 Relationships of Patients Factors, Leiomyoma Risk, and Steroid Hormones

Factor	Effect on Risk	Potential Reason
Postmenopausal	Decreased	Hypoestrogenism
Early menarche	Increased	Increased years of estrogen exposure
Obesity	Increased	Increased conversion of androgens to estrogens
Pregnancy	Decreased	Break in chronic estrogen exposure; uterine remodeling during postpartum involution
Combination oral contraceptives	Decreased	Exposure to estrogen opposed by progesterone
Cigarette smoking	Decreased	Decreased serum estrogen levels
African-American race	Increased	Genetic differences in hormone production or metabolism
Affected family member	Increased	Genetic differences in hormone production or metabolism

Modified from Cook, 2004, with permission.

Leiomyomas themselves create a hyperestrogenic environment, which appears requisite for their growth and maintenance. First, compared with normal myometrium, leiomyomas contain a greater density of estrogen receptors that results in greater estradiol binding. Secondly, these tumors convert less estradiol to the weaker estrone (Englund, 1998; Otubu, 1982; Yamamoto, 1993). A third mechanism described by Bulun and colleagues (1994) involves higher levels of cytochrome P450 aromatase in leiomyomas compared with normal myocytes. This specific cytochrome isoform catalyzes the conversion of androgens to estrogen in a number of tissues.

There are a number of conditions associated with increased estrogen production that encourage leiomyoma formation. For example, the increased years of estrogen exposure found with early menarche and with an increased body mass index (BMI) are each linked with a greater risk of leiomyomas (Marshall, 1998; Wise, 2005b). Obese women produce more estrogens from increased adipose conversion of androgens to estrogen and display decreased hepatic production of sex-hormone binding globulin (Glass, 1989).

Because pregnancy is a progesterone-dominant state, it should provide an interlude from chronic estrogen exposure, and intuitively at least, should discourage leiomyoma development. In support of this, women giving birth at an early age, those with higher parity, and those with a more recent pregnancy all display lower incidences of leiomyoma formation.

In premenopausal women, estrogen and progesterone hormone treatment probably has no inductive effect on leiomyoma formation. With few exceptions, oral contraceptive combination pills either lower or have no effect on this risk (Chiaffarino, 1999; Parazzini, 1992; Ross, 1986).

Most studies evaluating the effects of hormone replacement therapy, however, show either a stimulatory or no effect on growth (Polatti, 2000; Reed, 2004). Palomba and associates (2002) evaluated the relationship between leiomyoma growth and differing doses of medroxyprogesterone acetate (MPA) in hormone replacement therapy. Because higher doses of MPA were associated with leiomyoma growth, they recommended using the lowest possible dose of MPA in these patients.

Finally, smoking alters estrogen metabolism and lowers physiologically active serum estrogen levels (Daniel, 1992; Michnovicz, 1986). This may explain why women who smoke generally have a lower risk for leiomyoma formation (Parazzini, 1992).

Progestins

The role of progesterone in leiomyoma growth is less clear, and indeed both stimulatory and inhibitory effects have been reported. For example, exogenous progestins have been shown to limit leiomyoma growth in clinical trials (Goldzieher, 1966; Tiltman, 1985). Similarly, epidemiologic studies link depot medroxyprogesterone use with a lower incidence of leiomyoma development (Lumbiganon, 1996). In contrast, other studies report a stimulatory influence of progestins on leiomyoma growth. For example, the antiprogestin, mifepristone (RU486), induces atrophy in most leiomyomas (Murphy, 1993). Moreover, in women treated with gonadotropin-releasing hormone (GnRH) agonists, leiomyomas typically decrease in size. However, if progestins are given simultaneously with agonists, there may be *increased* leiomyoma growth (Carr, 1993; Friedman, 1994).

RISK FACTORS

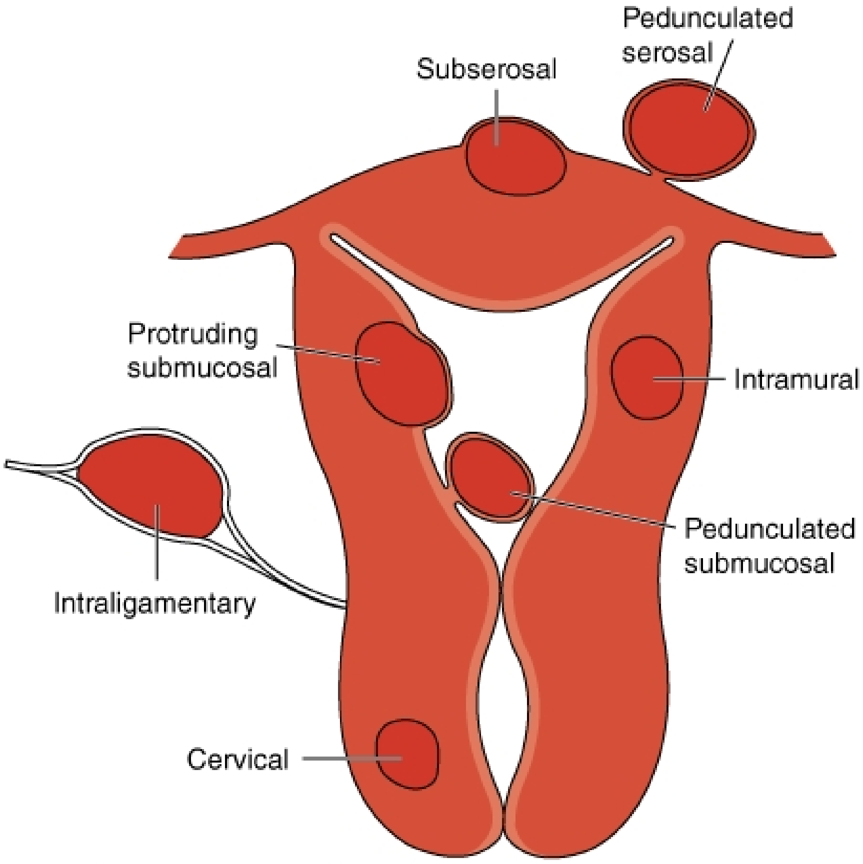
During the reproductive years, the incidence of this tumor increases with age. In a study by Day Baird and colleagues (2003), the cumulative incidence by age 50 years was nearly 70 percent in Caucasians and over 80 percent in African-American women. Sporadic case reports such as the one by Bekker and colleagues (2004) document their rarity in teenagers. After menopause, leiomyomas generally shrink in size, and new tumor development is uncommon. Thus, it seems that most risk or protective factors depend on circumstances that chronically alter estrogen or progesterone levels or both.

Leiomyomas are more common in African-American women compared with Caucasian, Asian, or Hispanic women. Few studies have been done to ascertain these ethnic differences (Amant, 2003; Woods, 1996). Heredity likely plays a role in susceptibility to the initial mutation involved with leiomyoma development. Family and twin studies have shown the risk of leiomyoma formation to be approximately two times greater in women with affected first-degree relatives (Sato, 2002; Vikhlyaeva, 1995).

CLASSIFICATION OF UTERINE LEIOMYOMAS

Leiomyomas are classified based on their location and direction of growth (Fig. 9-3). *Subserosal leiomyomas* originate from myocytes adjacent to the uterine serosa, and their growth is directed outward. When these are attached only by a stalk to their progenitor myometrium, they are called *pedunculated leiomyomas* . *Parasitic leiomyomas* are subserosal variants that attach themselves to nearby pelvic structures from which they derive vascular support, and then may or may not detach from the parent myometrium. *Intramural leiomyomas* are those with growth centered within the uterine walls. Finally, *submucous leiomyomas* are proximate to the endometrium and grow toward and bulge into the endometrial cavity. Only about 0.4 percent of leiomyomas develop in the cervix (Tiltman, 1998). Leiomyomas have also been found less commonly in the ovary, fallopian tube, broad ligament, vagina, and vulva.

FIGURE 9-3



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Leiomyomas can be described as submucous, subserosal, intramural, or pedunculated. The borders of most leiomyomas overlap these distinct regions.

Leiomyomatosis

Extrauterine smooth muscle tumors, which are benign yet infiltrative, may develop in women with concurrent uterine leiomyomas. This condition is termed *leiomyomatosis,* and its categorization is described below. In such cases, the diagnosis of malignant metastasis from a leiomyosarcoma must be excluded.

Intravenous leiomyomatosis is a rare, benign smooth muscle tumor that invades and extends serpiginously into the uterine and other pelvic veins, vena cava, and even cardiac chambers. Although histologically benign, the tumor can be fatal as a consequence of venous obstruction or cardiac involvement (Fang, 2007; Uchida, 2004).

Benign metastasizing leiomyomas derive from morphologically benign uterine leiomyomas which disseminate hematogenously. Lesions have been found in the lungs, gastrointestinal tract, spine, and brain (Alessi, 2003). Classically, these are found in women who have a recent or distant history of pelvic surgery (Zaloudek, 2002).

Disseminated peritoneal leiomyomatosis appears as multiple small nodules on the peritoneal surfaces of the abdominal cavity or the abdominal organs or both. They are usually found in women of reproductive age, and 70 percent are associated with pregnancy or combination oral contraceptives (Robboy, 2000).

Treatments for these three benign conditions involve hysterectomy with oophorectomy, tumor debulking, and more recently, use of GnRH agonists, aromatase inhibitors, and selective estrogen receptor modulators (Bodner, 2002; Rivera, 2004; Sobiczewski, 2004).

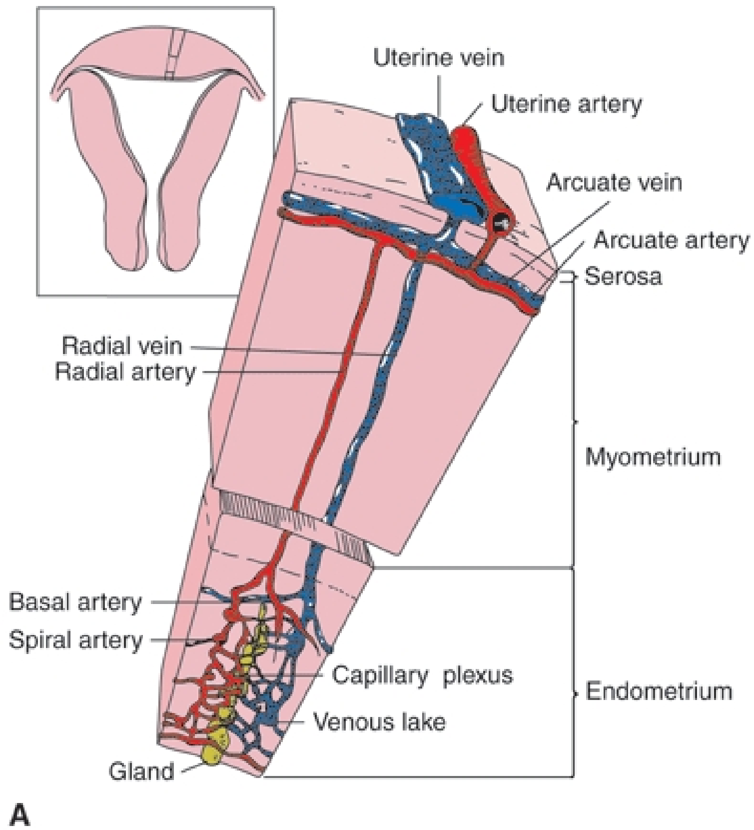
SYMPTOMS

Most women with leiomyomas are asymptomatic. However, symptomatic patients typically complain of bleeding, pain, pressure sensation, or infertility. In general, the larger the leiomyoma, the greater the likelihood of symptoms (Cramer, 1990).

Bleeding

This is the most common symptom and usually presents as menorrhagia (Olufowobi, 2004). The pathophysiology underlying this bleeding may relate to dilatation of venules. Bulky tumors are thought to exert pressure and impinge on the uterine venous system, which causes venular dilatation within the myometrium and endometrium (Figs. 9-4 and 9-5). Accordingly, intramural and subserosal tumors have been shown to have the same propensity to cause menorrhagia as submucous ones (Wegienka, 2003).

FIGURE 9-4



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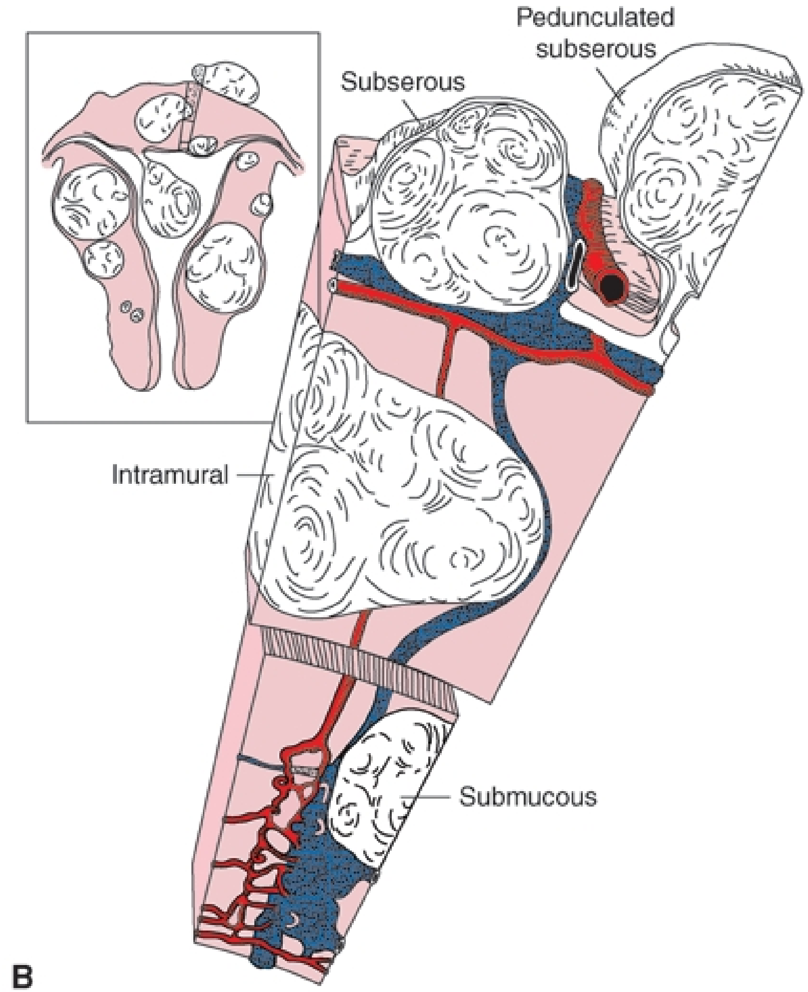

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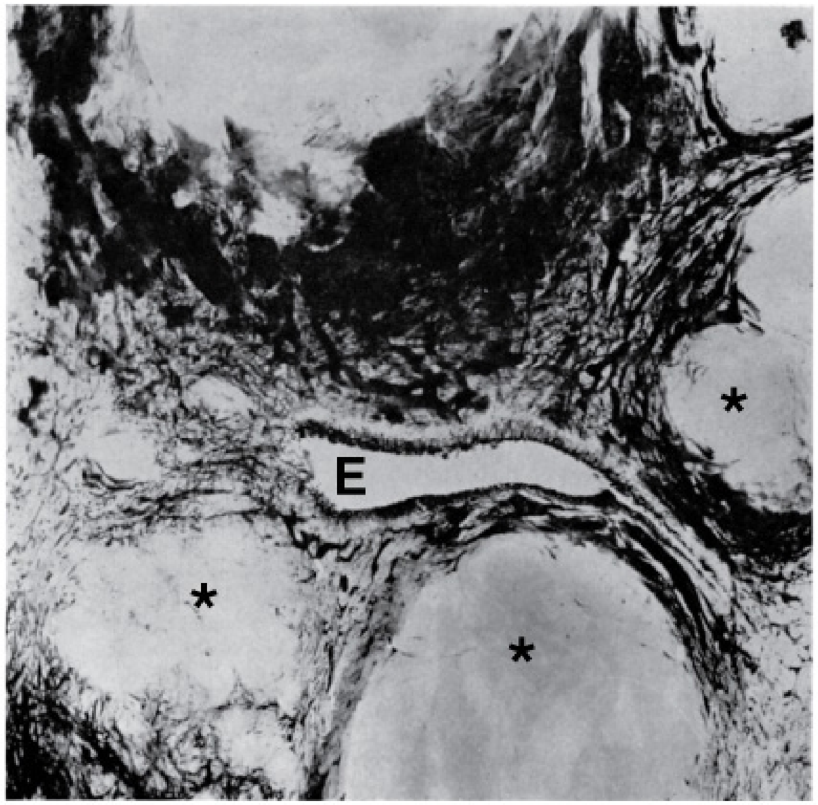
A. Normal uterine vasculature. Anatomy of the myometrium and endometrium is an expanded view of the wedge taken from the uterus shown in the inset. **B.** At any level within the myometrium, submucous, subserosal, and intramural leiomyomas can compress adjacent veins and thereby cause dilatation of distal endometrial venules. *(Redrawn from Buttram, 1981.)*

FIGURE 9-5



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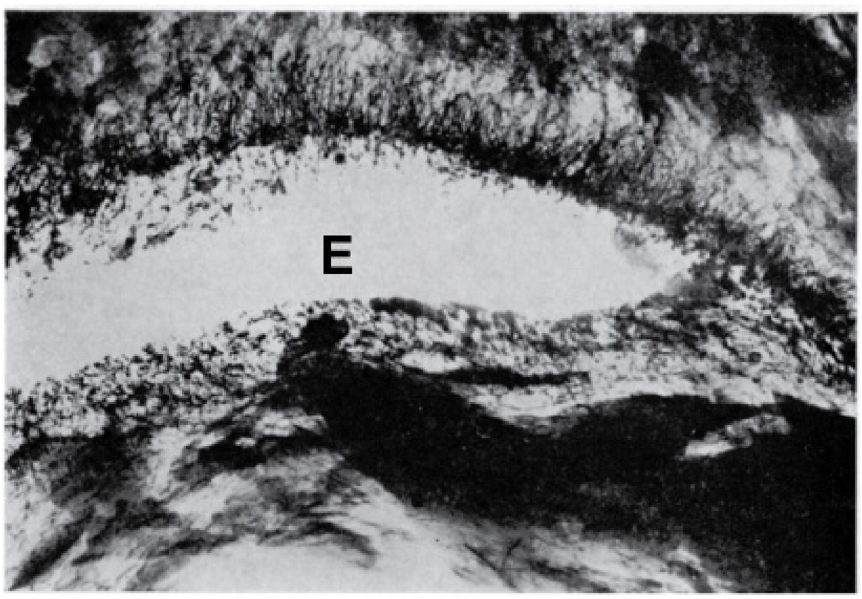

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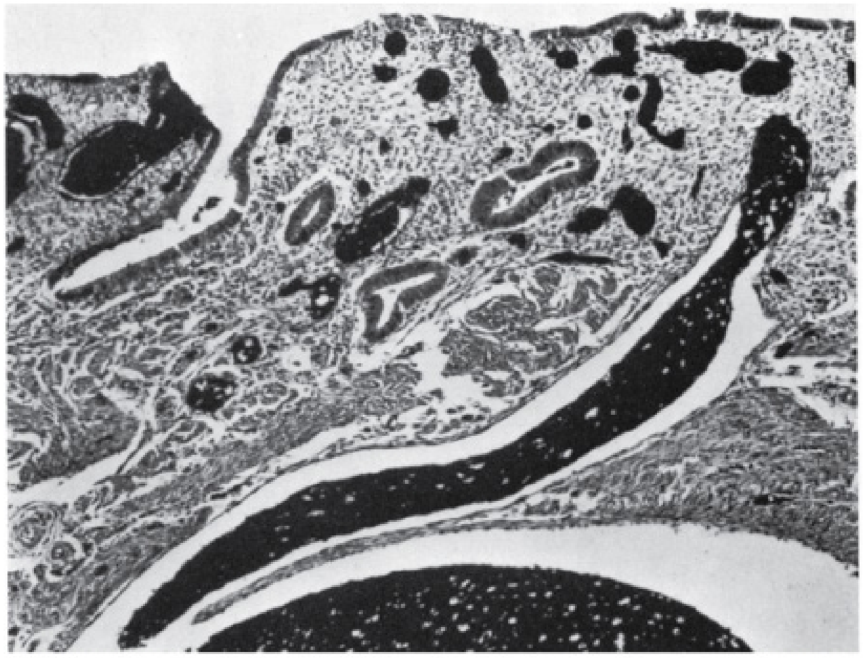


C

Histology of uterine vasculature following venous injection of dye to highlight vascular anatomy. **A.** Transverse section through uterine myometrium and endometrium. Dilated venous plexuses around the leiomyomas are seen as a black network. Note the multiple leiomyomas (**black asterisks**) and endometrial cavity (E). **B.** Higher magnification showing black dilated veins in the base of the endometrium. **C.** Highest magnification shows dilated endometrial venules, which communicate with an enlarged vessel in the inner myometrium. With menses and sloughing of the functionalis layer, greater bleeding follows disruption of these dilated venules. *(From Farrer-Brown, 1970, 1971, with permission.)*

Dysregulation of local vasoactive growth factors are also thought to promote vasodilatation. When engorged venules are disrupted at the time of menstrual sloughing, bleeding from the markedly dilated venules overwhelms usual hemostatic mechanisms (Stewart, 1996).

Pelvic Discomfort and Dysmenorrhea

A sufficiently enlarged uterus can cause pressure sensation, urinary frequency, incontinence, and constipation. Rarely, leiomyomas extend laterally to compress the ureter and lead to obstruction and hydronephrosis. Although dysmenorrhea is common, in a population-based cross-sectional study, Lippman and co-workers (2003) reported that women with leiomyomas more frequently had dyspareunia or noncyclical pelvic pain than dysmenorrhea.

INFERTILITY AND PREGNANCY WASTAGE

Although the mechanisms are not clear, leiomyomas can be associated with infertility. It is estimated that 2 to 3 percent of infertility cases are due solely to leiomyomas (Buttram, 1981; Kupesic, 2002). Their putative effects include occlusion of tubal ostia and disruption of the normal uterine contractions that propel sperm or ova. Distortion of the endometrial cavity may diminish implantation and sperm transport. Importantly, leiomyomas are associated with endometrial inflammation and vascular changes that may disrupt implantation (American Society for Reproductive Medicine, 2004a; Brosens, 2003; Farhi, 1995).

There is a stronger association of subfertility with submucous leiomyomas than with tumors located elsewhere. Improved pregnancy rates following hysteroscopic resection have provided most of the indirect evidence for this link (Vercellini, 1999). In one study, Garcia and Tureck (1984) reported pregnancy rates approaching 50 percent following myomectomy in women with

submucous leiomyomas as their sole source of infertility.

The relationship between subfertility and intramural and subserosal leiomyomas that do not distort the endometrial cavity is more tenuous. A number of investigators have reported equally good in vitro fertilization success rates in women with and without leiomyomas that did not distort the endometrial cavity (Farhi, 1995; Oliveira, 2004). Others, however, have reported adverse fertility effects from even intramural and subserosal leiomyomas (Hart, 2001; Marchionni, 2004).

Both uterine leiomyoma and spontaneous miscarriage are common, and an association between these has not been shown convincingly. Indirect evidence comes from studies that cite significantly lower abortion rates following resection (Campo, 2003; Vercellini, 1999).

Other Clinical Manifestations

Less than 0. 5 percent of women with leiomyomas develop *myomatous erythrocytosis syndrome* . This may result from excessive erythropoietin production by the kidneys or by the leiomyomas themselves (Kohama, 2000; Yokoyama, 2003). In either case, red cell mass returns to normal following hysterectomy.

Leiomyomas occasionally may cause *pseudo-Meigs syndrome* . Traditionally, Meigs syndrome consists of ascites and pleural effusions that accompany benign ovarian fibromas. However, any pelvic tumor including large, cystic leiomyomas or other benign ovarian cysts can cause this. The presumed etiology stems from discordancy between the arterial supply to and the venous and lymphatic drainage from leiomyomas. Resolution of ascites and hydrothorax follows hysterectomy.

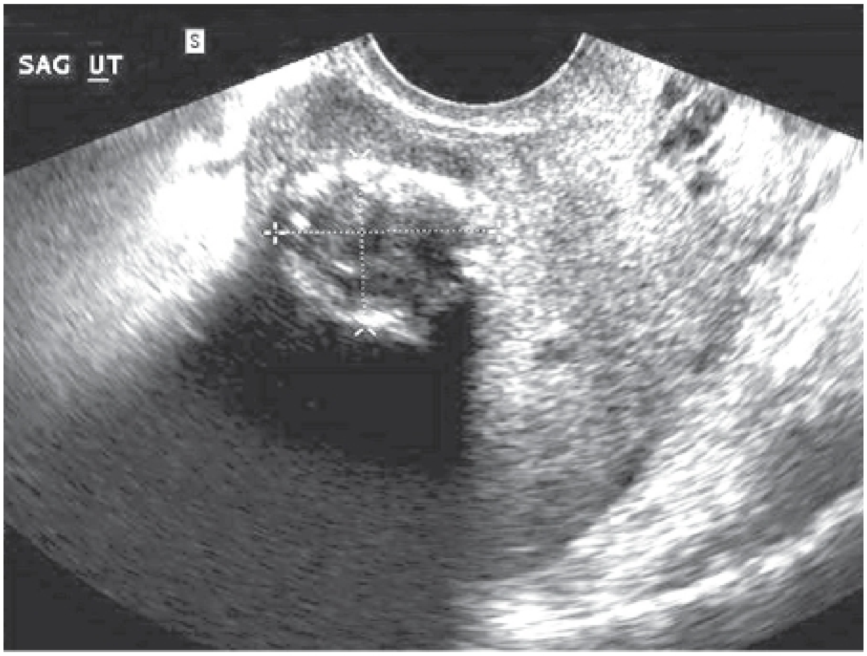
DIAGNOSIS

Leiomyomas are often detected by pelvic examination with findings of uterine enlargement, irregular contour, or both. In reproductive-aged women, uterine enlargement should prompt determination of a urine or serum β-hCG level.

Imaging

Sonography is initially done to define pelvic anatomy. The sonographic appearances of leiomyomas vary from hypo- to hyperechoic, depending on the ratio of smooth muscle to connective tissue and whether there is degeneration. Calcification and cystic degeneration create the most sonographically distinctive changes (Fig. 9-6). Calcifications appear hyperechoic and commonly rim the tumor or are randomly scattered (Kurtz, 1979). Cystic or myxoid degeneration typically fills the leiomyoma with multiple, smooth-walled, round, irregularly sized but generally small hypoechoic areas.

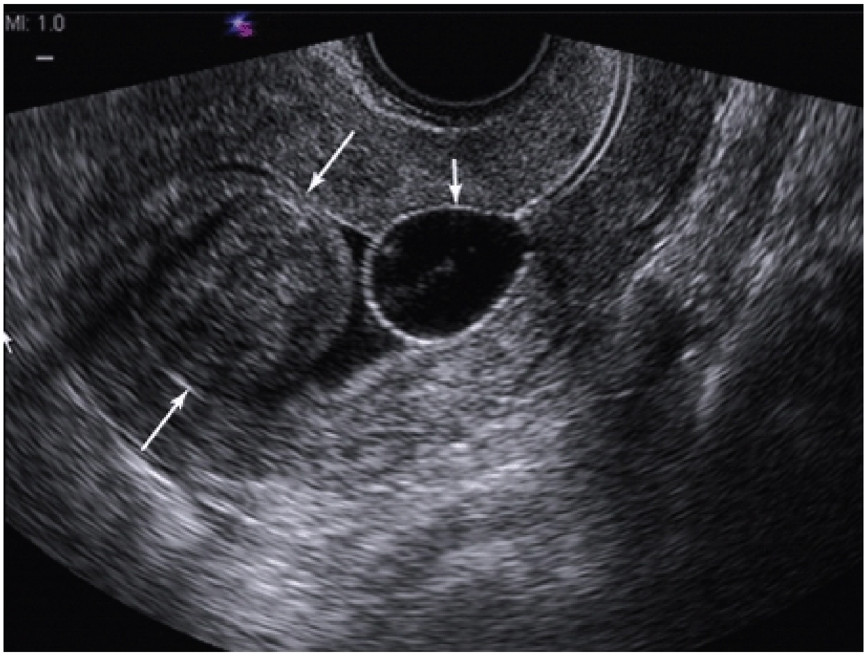
FIGURE 9-6



Transvaginal sonogram of an intramural leiomyoma with calcified border. *(Courtesy of Dr. Elysia Moschos.)*

If menorrhagia, dysmenorrhea, or infertility accompanies a pelvic mass, then the endometrial cavity should be evaluated for submucous leiomyomas, endometrial polyps, congenital anomalies, or synechiae (Fig. 9-7). Accordingly, saline-infusion sonography (SIS), hysteroscopy, and hysterosalpingography (HSG) may have a role. Weinraub and associates (1996) reported use of three-dimensional SIS, however, any clear advantage over two-dimensional SIS or hysteroscopy has not been demonstrated (de Kroon, 2004).

FIGURE 9-7



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Submucous fibroid clearly outlined by saline-infusion sonography and identified by long white arrows. The SIS catheter balloon is indicated by the short white arrow. *(Courtesy of Dr. Elysia Moschos.)*

Leiomyomas have characteristic vascular patterns that can be identified by color flow Doppler. A peripheral rim of vascularity from which a few vessels arise to penetrate into the center of the tumor is traditionally seen. Doppler imaging can be used to differentiate an extrauterine leiomyoma from other pelvic masses or a submucous leiomyoma from an endometrial polyp or adenomyosis (see Chap. 8, Transvaginal Color Doppler Sonography) (Fleischer, 2003).

Magnetic resonance (MR) imaging may be required when imaging is limited by body habitus or distorted anatomy. This tool allows more accurate assessment of the size, number, and location of leiomyomas, which may help identify appropriate patients for alternatives to hysterectomy, such as myomectomy or uterine artery embolization (see Fig. 2-25) (Zawin, 1990).

MANAGEMENT

Observation

Regardless of their size, asymptomatic leiomyomas usually can be managed expectantly by annual pelvic examination (American College of Obstetricians and Gynecologists 2001). If assessment of the adnexa is hindered by uterine size or contour, some may choose to add annual sonographic surveillance (Guarnaccia, 2001).

In the past, most preferred surgical removal of a large, asymptomatic leiomyomatous uterus because of concerns regarding increased operative morbidity and cancer risks. These have been disproven, and thus otherwise asymptomatic women with large leiomyomas can also be managed expectantly (Parker, 1994; Stovall, 1994). In addition, most infertile women with uterine leiomyomata are management expectantly. For those with symptomatic tumors, surgery should be timed closely to planned pregnancy, if possible, to limit the risk of leiomyoma recurrence.

Drug Therapy

In some women with symptomatic leiomyomas, medical therapy may be preferred (Table 9-2). In addition, because leiomyomas typically regress postmenopausally, some women choose medical treatment to relieve symptoms in anticipation of menopause. In others, medical therapy, such as GnRH agonists, are used as a preoperative adjunct to surgery.

Table 9-2 Indications for the Medical Treatment of Uterine Leiomyoma			
Symptom	**NSAIDs**	**COCs**	**Short-Term Administration of GnRH Agonist (perimenopausally or preoperatively only)**
Dysmenorrhea	+	+	+
Menorrhagia	â€“	+	+
Dyspareunia	â€“	â€“	+
Pelvic pressure	â€“	â€“	+
Infertility	â€“	â€“	+

COCs = combination oral contraceptive pills; GnRH = gonadotropin-releasing hormone; NSAIDs = nonsteroidal anti-inflammatory drugs.

Nonsteroidal Anti-Inflammatory Drugs

Women with dysmenorrhea have higher endometrial levels of prostaglandins F_2 and E_2 than asymptomatic women (Willman, 1976; Ylikorkala, 1978). Accordingly, treatment of dysmenorrhea and menorrhagia associated with leiomyomas is based on the role of prostaglandins as mediators of these symptoms. A number of NSAIDs have proved effective for dysmenorrhea, yet there is not one considered to be superior (Table 10-2). Prostaglandins are also associated with menorrhagia (see Chap. 8, Nonsteroidal Anti-Inflammatory Drugs) (Willman, 1976). That said, benefits of NSAIDs for leiomyoma-related bleeding are less clear. The few studies done have had conflicting results (Anteby, 1985; Makarainen, 1996; Ylikorkala, 1986). Available data do not support their use as sole agents for leiomyoma-related menorrhagia.

Hormonal Therapy

Both combination oral contraceptive pills (COCs) and progestins have been used to induce endometrial atrophy and decrease prostaglandin production in women with leiomyomas. Friedman and Thomas (1995) studied 87 women with leiomyomas and reported that those taking low-dose COCs had significantly shorter menses and no evidence of uterine enlargement. Orsini and colleagues (2002) reported similar results.

There are conflicting results from trials of the levonorgestrel-releasing intrauterine device (Mirena, Berlex, Wayne, NJ) to treat leiomyoma-related menorrhagia. Although, Grigorieva and co-workers (2003) reported reduced blood loss and improved hematocrits in these women, Mercorio and associates (2003) did not confirm these findings.

Because of unpredictable effects of progestins on leiomyoma growth with the potential to worsen symptoms, the American Society for Reproductive Medicine (2004a) does not recommend either progestins or combination COCs for leiomyoma-related symptoms.

Androgens

Both danazol and gestrinone have been found to shrink leiomyoma volume and improve bleeding symptoms (Coutinho, 1989; De Leo, 1999). Unfortunately, their prominent side effects, which include acne and hirsutism, preclude their use as first-line agents (see Chap. 10, Androgens).

GnRH Agonists

These compounds are synthetic derivatives of the GnRH decapeptide. Amino-acid substitution makes them resistant to degradation, thereby increasing their half-life and resulting in prolonged receptor binding. They are inactive if taken orally, but intramuscular, subcutaneous, and intranasal preparations are available. A number of GnRH agonists that have been studied in clinical trials are shown in Table 9-3. There is no evidence to support the superiority of one of these regimens over the others for leiomyoma treatment (Chavez, 2001).

Table 9-3 Dosages of Gonadotropin-Releasing Hormone Agonists		
Brand Name	**Generic Name**	**Dosage**
Decapeptyl	Triptorelin	3.75 mg depot IM monthly
Lupron	Leuprolide acetate	3.75 mg depot IM monthly
Zoladex	Goserelin	3.6 mg depot SC monthly
Synarel	Nararelin	200 mg taken twice daily as one spray into one nostril in the morning and one spray into the other nostril in the evening

IM = intramuscularly; SC = subcutaneously.

These drugs shrink leiomyomas by targeting the growth effects of estrogen and progesterone. They initially stimulate receptors on pituitary gonadotropes to cause a supraphysiologic release of both luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Also called a *flare* , this phase typically lasts 1 week. With their long-term action, however, agonists downregulate receptors in gonadotropes, thus creating desensitization to further GnRH stimulation. Correspondingly, decreased gonadotropin secretion leads to suppressed estrogen and progesterone levels 1 to 2 weeks after initial GnRH agonist administration (Broekmans, 1996). Another possible mechanism is that leiomyomas themselves may contain GnRH receptors, and agonists may directly decrease leiomyoma size (Chegini, 1996; Parker, 2007; Wiznitzer, 1988).

Results with GnRH agonist treatment include dramatic decreases in uterine and leiomyoma volume. Most women experience a mean decrease in uterine volume of 40 to 50 percent, with most shrinkage occurring during the first 3 months of therapy. Clinical benefits of reduced leiomyoma volumes include pain relief and diminished menorrhagia, usually amenorrhea. During this time, anemic women are given oral iron therapy to repair red cell mass and increase iron stores (Filicori, 1983; Friedman, 1990). Most recommend treatment for a total of 3 to 6 months. Following their discontinuance, normal menses resume in 4 to 10 weeks. Unfortunately, leiomyomas then regrow and uterine volumes regain pretreatment sizes within 3 to 4 months (Friedman, 1990). Despite regrowth, Schlaff and co-workers (1989) reported symptom relief for about 1 year in half of women given GnRH agonists.

GnRH agonists have significant costs, risks, and side effects. Side effects result from a profound drop in serum estrogen levels and include vasomotor symptoms, libido changes, and vaginal epithelium dryness and accompanying dyspareunia. Importantly, 6 months of agonist therapy can result in a 6 percent loss in trabecular bone, not all of which may be recouped following discontinuation (Scharla, 1990). As a result, these agents are not recommended for use longer than 6 months.

To obviate the severity of these side effects, several medications have been added to GnRH agonist treatment. The goal of this "add-back therapy" is to counter side effects without mitigating the effects on uterine and leiomyoma volume decrease. Mizutani and co-workers (1998) found that GnRH agonists suppress leiomyoma cell proliferation and induce cell apoptosis at the fourth week of GnRH agonist therapy. They proposed that add-back therapy be withheld until after this time threshold. Because of these and other observations, add-back therapy is typically begun 1 to 3 months following GnRH agonist initiation.

Add-back therapy traditionally includes estrogen combined with a progestin. A regimen of medroxyprogesterone acetate (MPA) 10 mg (days 16 to 25 of each cycle), combined with equine estrogen 0.625 mg (days 1 to 25), or a continuous daily regimen of MPA 2.5 mg and equine estrogen 0.625 mg may be used.

Add-back therapy with selective estrogen receptor modulators (SERMs), such as tibolone and raloxifene, has also been shown to prevent bone loss. Advantages of SERMs include the ability to begin them concurrently with GnRH agonist treatment without negating the agonist effects of leiomyoma shrinkage. Unfortunately, a high percentage of women complain of vasomotor symptoms while taking SERMs (Palomba, 1998, 2004).

Because of the limitations of GnRH agonist therapy, the American College of Obstetricians and Gynecologists (2001) currently

recommends it only as a temporizing agent in women nearing menopause or as surgical pretreatment in selected women.

Preoperatively, GnRH agonists offer several advantages. Their use decreases menorrhagia and may allow correction of anemia. Decreased uterine size as a result of treatment may allow a less-complicated or extensive surgical procedure. For example, hysterectomy or myomectomy may be performed through a smaller laparotomy incision or by vaginal hysterectomy, laparoscopy, or hysteroscopy (Crosignani, 1996; Mencaglia, 1993; Stovall, 1994). A fuller discussion of preoperative GnRH agonist use can be found in Section 41-18, Myomectomy.

GnRH Antagonists

Synthetically derived GnRH antagonists have also been studied for treatment of leiomyomas. Although their profound hypoestrogenic effects are similar to those of GnRH agonists, they avoid the initial gonadotropin flare and have a more rapid action. Studies have evaluated cetrorelix and also Nal-glu, so named because of its glutamatic acid structural substitution of the original GnRH structure. Daily subcutaneous injections induce leiomyoma shrinkage comparable with GnRH agonists (Gonzalez-Barcena, 1997; Kettel, 1993). A depot form of cetrorelix, however, did not provide adequate or consistent suppression of estrogen production or leiomyoma growth (Felberbaum, 1998).

Antiprogestins

Mifepristone, also known as RU486, is the most widely available antiprogestin for treatment of leiomyomas. It has proved effective in decreasing leiomyoma volume and clinical symptoms.

Progesterone binds to either progesterone receptor A or B (PR-A, PR-B). Mifepristone exerts its effects mainly through PR-A, which is found in leiomyomas in greater amounts than PR-B (Viville, 1997). Mifepristone diminishes leiomyoma volume by approximately half. Various doses have been used and include 5, 10, 25, or 50 mg given orally daily during 12 weeks (Eisinger, 2003; Murphy, 1993). In their review, Steinauer and colleagues (2004) found that although there was not a consistent correlation between increasing mifepristone dose and leiomyoma response, increasing duration of treatment did correlate with tumor shrinkage during 3- to 6-month trials. They also reported that mifepristone was effective in improving symptoms. Of those treated, 91 percent developed amenorrhea, 75 percent reported improved pain relief, and 70 percent had fewer pressure symptoms. In a comparison of leuprolide acetate treatment and mifepristone therapy, Reinsch and associates (1994) showed comparable decreases in uterine volume, yet mifepristone was better tolerated.

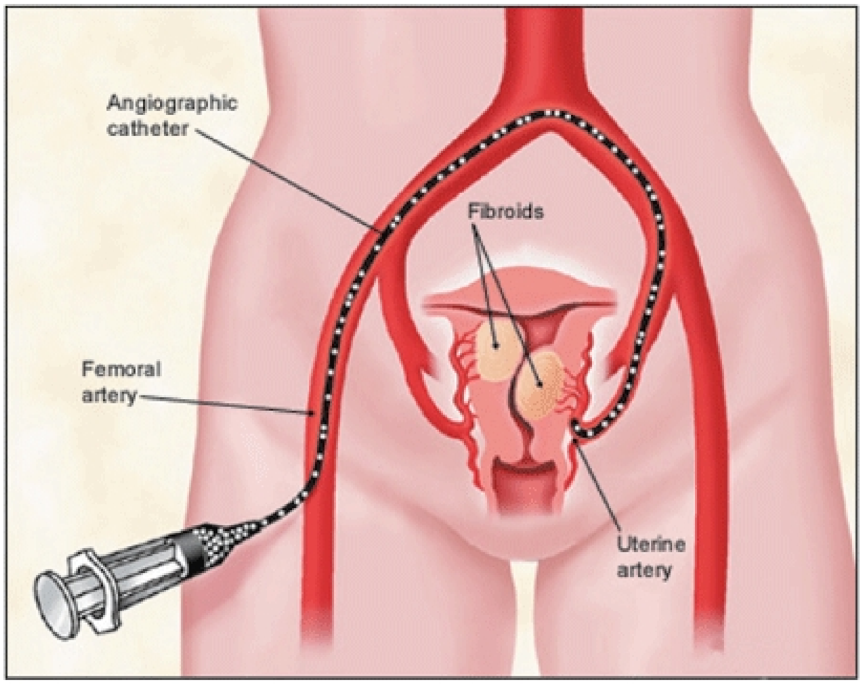
Mifepristone therapy, however, has several drawbacks. Approximately 40 percent of treated women complain of vasomotor symptoms. Antiprogestational effects expose the endometrium to unopposed estrogen, and Eisinger and associates (2003) found simple hyperplasia in 28 percent of 36 women sampled. Serum levels of hepatic transaminases become elevated in about 4 percent of women, but these return to normal after discontinuation in virtually all (Steinauer, 2004). Despite its antiglucocorticoid potential, increased serum cortisol levels are unusual with mifepristone, and if elevated they revert to normal after discontinuation (Reinsch, 1994).

Uterine Artery Embolization

This is an angiographic interventional procedure that delivers polyvinyl alcohol (PVA) microspheres or other particulate emboli into both uterine arteries. Uterine blood flow is therefore obstructed, producing ischemia and necrosis. Because vessels serving leiomyomas have a larger caliber, these microspheres are preferentially directed to the tumors, sparing the surrounding myometrium.

An angiographic catheter is placed in either femoral artery and advanced under fluoroscopic guidance to selectively catheterize both uterine arteries (Fig. 9-8). Failure to embolize both uterine arteries allows existing collateral circulation between the two uterine arteries to sustain leiomyoma blood flow and is associated with a significantly poorer outcome.

FIGURE 9-8



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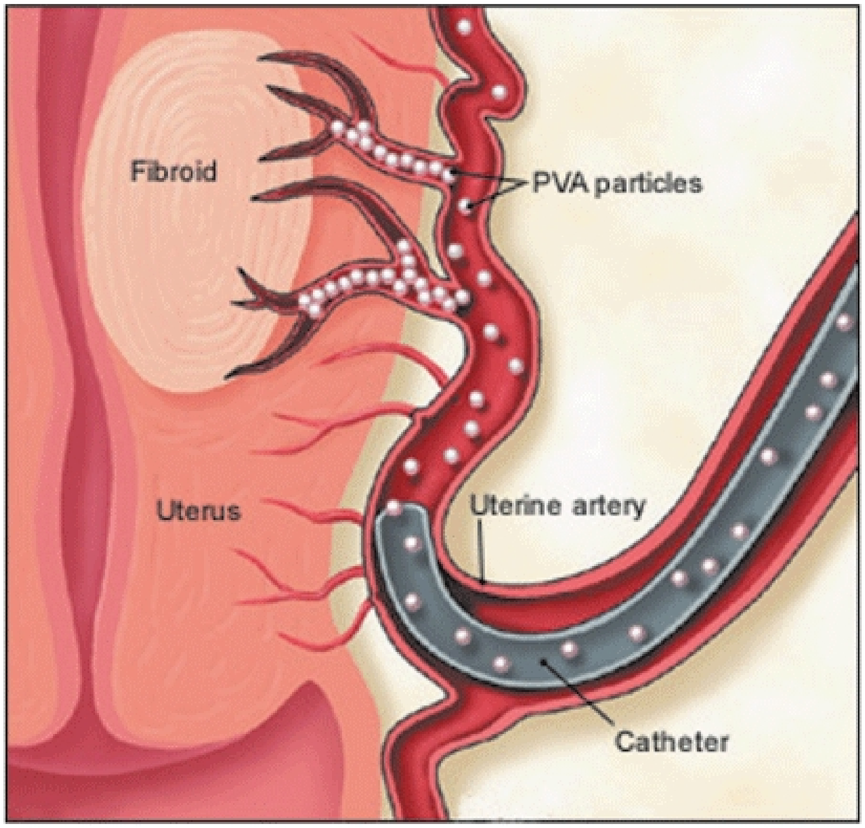
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



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Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Diagram of uterine artery embolization. PVA = polyvinyl alcohol. *(From Smith, 2000, with permission.)*

As a result of leiomyoma necrosis, there typically are significant postprocedural symptomsâ€”the *postembolization syndrome.* This usually lasts 2 to 7 days, and it is classically marked by pelvic pain and cramping, nausea and vomiting, low-grade fever, and malaise. Intensity of these symptoms varies, and pain management strategies include oral, intravenous, epidural, or patient-controlled analgesia regimens (Hovsepian, 2004).

Embolization is effective for leiomyoma-related symptoms. Pron and associates (2003) followed 538 women after UAE and found a clinical success rate of 80 percent for bleeding and pain and 91 percent for patient satisfaction. In addition, for most, UAE is associated with shorter hospital stays and quicker postoperative recovery than hysterectomy. However, rates of readmission and further treatment for bleeding are higher with UAE (Edwards, 2007; Hehenkamp, 2005; Pinto, 2003). Long-term data following UAE are limited. Broder and co-workers (2002) re-evaluated a group of these women 5 years postprocedure and reported that 27 percent had required further invasive treatment(s) for their leiomyomas. The American College of Obstetricians and Gynecologists (2004) currently recommends UAE for short-term relief of bleeding or pressure symptoms.

There are a number of complications associated with UAE. Leiomyoma tissue passage is common and likely is seen only with leiomyomas that have contact with the endometrial surface. Necrotic tissue that passes into the vagina usually can be removed in the office. Those that do not pass spontaneously or that remain firmly attached to the uterine wall may require dilatation and evacuation (Spies, 2002). Transient amenorrhea, which lasts at most a few menstrual cycles, is also commonly seen following UAE and is not typically associated with increased FSH levels or menopausal symptoms. Permanent amenorrhea, however, develops occasionally. Rarely, serious complications occur following embolization and include necrosis of surrounding tissues such as the uterus, adnexa, bladder, and soft tissues.

A number of complications have been identified in women during pregnancy subsequent to UAE. Goldberg and colleagues (2004) reported increased risks for preterm delivery and malpresentation in women who were treated by UAE when compared with pregnancies that followed laparoscopic myomectomy. Increased incidence of abnormal placentation has also been identified (Pron, 2005). Due to lack of long-term outcome data, women who desire future childbearing are not currently considered candidates for UAE (American College of Obstetricians and Gynecologists, 2004).

As discussed in Chapter 2, preliminary studies indicate that magnetic resonance imagingâ€"guided focused ultrasound (MRI-FUS) therapy is a safe and feasible, minimally invasive alternative for leiomyoma treatment (Chen, 2005; Fennessy, 2007; Stewart, 2003, 2006). It may provide short-term symptom relief with the advantage of a quicker recovery and few major adverse events. However, little information is available on the costs and comparisons with other treatments such as UAE.

Surgical Management

Bleeding and pain symptoms may improve in many women using medical treatment or UAE. However, for many, surgical treatments for leiomyomas are necessary and include hysterectomy, myomectomy, and myolysis.

Hysterectomy

Removal of the uterus is the definitive and most common surgical treatment for leiomyomas. Hysterectomy for leiomyoma can be performed vaginally, abdominally, or laparoscopically. Between 1994 and 1999, more than 3.5 million hysterectomies were performed in the United States, and almost a third were performed for the diagnosis of uterine leiomyoma (Keshavarz, 2002). In a study of 418 women undergoing hysterectomy for benign gynecologic conditions, Carlson and co-workers (1994) found hysterectomy for women with symptomatic leiomyomas resulted in satisfaction rates greater than 90 percent. There were marked improvements in pelvic pain, urinary symptoms, fatigue, psychological symptoms, and sexual dysfunction.

Removal of the ovaries is not required, and the decision to perform oophorectomy at the time of hysterectomy is made based on the usual factors (see Section 41-19, Hysterectomy). Other considerations prior to hysterectomy include uterine size and preoperative hematocrit. In some cases, preoperative GnRH agonist use may provide advantages.

Myomectomy

Resection of tumors is an option for symptomatic women who desire future childbearing or for those who decline hysterectomy. This can be performed laparoscopically, hysteroscopically, or via laparotomy incision and are described in Section 41-18, Myomectomy.

Myomectomy usually improves pain, infertility, or bleeding. For example, menorrhagia improves in approximately 70 to 80 percent of patients (Buttram, 1981; Olufowobi, 2004).

Myomectomy versus Hysterectomy

Historically, hysterectomy has been recommended for women not seeking pregnancy. Many believed that myomectomy, compared with hysterectomy, carried a greater risk for perioperative morbidity. As experience accrued, myomectomy has been shown to be effective and to carry perioperative risks comparable with hysterectomy. In a number of reports, blood loss, intraoperative injuries, and febrile morbidity were similar (Iverson, 1996; Sawin, 2000).

Disadvantageously, postoperative intra-abdominal adhesions and leiomyoma recurrence are more common after myomectomy compared with hysterectomy (Stricker, 1994). Recurrence rates following myomectomy range from 40 to 50 percent (Acien, 1996; Fedele, 1995). New leiomyoma development, however, appears diminished in women who become pregnant following myomectomy, perhaps because of protective effects of increasing parity (Candiani, 1991).

Laparoscopic Myomectomy

Laparoscopic leiomyoma resection may be performed with successful outcomes (Hurst, 2005; Mais, 1996). In one study, Seracchioli and co-workers (2000) reviewed results of 131 women following myomectomy for at least one large leiomyoma. They reported equivalent pregnancy rates with fewer transfusions, shorter hospital stays, and less febrile morbidity in women undergoing laparoscopic resection compared with laparotomy. Moreover, laparoscopic myomectomy appears to incite less adhesion formation than with laparotomy (Bulletti, 1996; Dubuisson, 2000; Takeuchi, 2002).

Limitations to a laparoscopic approach, however, include uterine size and laparoscopic surgical skills, especially suturing techniques. Most advocate a one- or two-layer suture closure of leiomyoma beds following enucleation (Seinera, 1997). In addition, several investigators have recommended limiting resection to those tumors less than 8 to 10 cm because of increased hemorrhage and operating time with larger tumors (Dubuisson, 2001; Takeuchi, 2003).

There are risks associated with laparoscopic myomectomy. Excision sites have been associated with uteroperitoneal fistula or with uterine rupture during subsequent pregnancy (Nezhat, 1996). At times, laparoscopic technique requires conversion to laparotomy due to bleeding or difficult tumor enucleation. It is unclear whether laparoscopic myomectomy is associated with greater risk of recurrence. Rossetti and co-workers (2001) found equivalent rates of leiomyoma recurrence with laparotomy or laparoscopic myomectomy, whereas Nezhat and colleagues (1998) found higher rates following laparoscopy.

Hysteroscopy

Resection of submucous leiomyomas through a hysteroscope has long-term effectiveness of 60 to 90 percent for the treatment of menorrhagia (Derman, 1991; Emanuel, 1999; Hallez, 1995). Hysteroscopic leiomyoma resection also improves fertility rates, especially when tumors are the sole cause of infertility (Fernandez, 2001; Vercellini, 1999). In their review, Donnez and Jadoul (2002) calculated an overall pregnancy rate of 45 percent following hysteroscopic tumor resection in women with leiomyoma as their sole identified source of infertility.

Endometrial Ablation

There are several tissue destructive modalities that ablate the endometrium and they are discussed in detail in Section 41-36, Endometrial Ablation Procedures. These techniques are effective for women with dysfunctional uterine bleeding, but when used as a sole technique for leiomyoma-related bleeding, the failure rate approaches 40 percent (Goldfarb, 1999; Yin, 1998). In some cases, ablation is used as an adjunct to hysteroscopic leiomyoma resection in women with menorrhagia.

Myolysis

A number of techniques are available to induce leiomyoma necrosis and shrinkage and include mono- or bipolar cautery, laser vaporization, or cryotherapy. All of these techniques are used laparoscopically and consume a great deal of operating room time, incite variable degrees of necrosis within the leiomyoma and surrounding normal myometrium, and produce significant postoperative pain. Data regarding long-term symptom relief, recurrence rates, and effects on fertility and pregnancy are lacking. Until clinical trials are done, these are currently considered experimental.

Hematometra

In this condition, menstrual outflow obstruction at the level of the cervix or higher traps blood and distends the uterus.

PATHOGENESIS

Many cases of hematometra develop at menarche when menstrual flow is obstructed by congenital anomalies (see Chap. 18, Description and Patient Presentation). In this setting, hematocolpos, that is, trapped blood that distends the vagina is also commonly associated and hematosalpinx may be seen.

A number of acquired abnormalities such as scarring and neoplasms can also obstruct menstrual flow. For example, hematometra may follow surgeries of the endometrial or endocervical canal, radiation treatment, and prolonged hypoestrogenism with atrophy. Similarly, it may develop in those with Asherman syndrome or with malignancies of the uterus or cervix.

DIAGNOSIS

Women with hematometra classically complain of cyclic, midline pain. With total obstruction, there is amenorrhea. Partial obstruction causes pain accompanied by scant dark bleeding that may have a foul odor and may not be cyclic. If secondary infection and pyometra develop, fever and tachycardia may be noted. Findings on examination include an enlarged, soft or even cystic midline uterine corpus that may be tender to palpation. Clinical findings may mimic early pregnancy, cystic degeneration of leiomyomas, leiomyosarcoma, and gestational trophoblastic disease. Thus, urine or serum β-hCG assay may helpful. In cases in which the underlying cause is unclear, endocervical and endometrial biopsy is indicated to exclude malignancy.

Sonography is the principal diagnostic tool, and imaging shows a smooth, symmetric hypoechoic enlargement of the uterine cavity. Low-level internal echoes may variably be present (Wu, 1999). A hematosalpinx is seen less commonly and is identified as hypoechoic tubular distensions lateral to a hypoechoic uterus (Sailer, 1979).

TREATMENT

For most cases of hematometra, relief of the obstruction and evacuation of blood are the goals. Cervical dilatation usually relieves the accumulation (Borten, 1984). Some have described hysteroscopy following dilatation to access blood pockets and to lyse adhesions (Cooper, 2000). Congenital abnormalities may require more extensive procedures to correct the obstruction (see Chap. 18, Diagnosis and Treatment).

Adenomyosis

Adenomyosis is characterized by uterine enlargement caused by ectopic rests of endometrium located deep within the myometrium. These rests may be scattered throughout the myometriumâ€"*diffuse adenomyosis* â€"or they may form a circumscribed nodular focal collection with a pseudocapsuleâ€"*focal adenomyosis* .

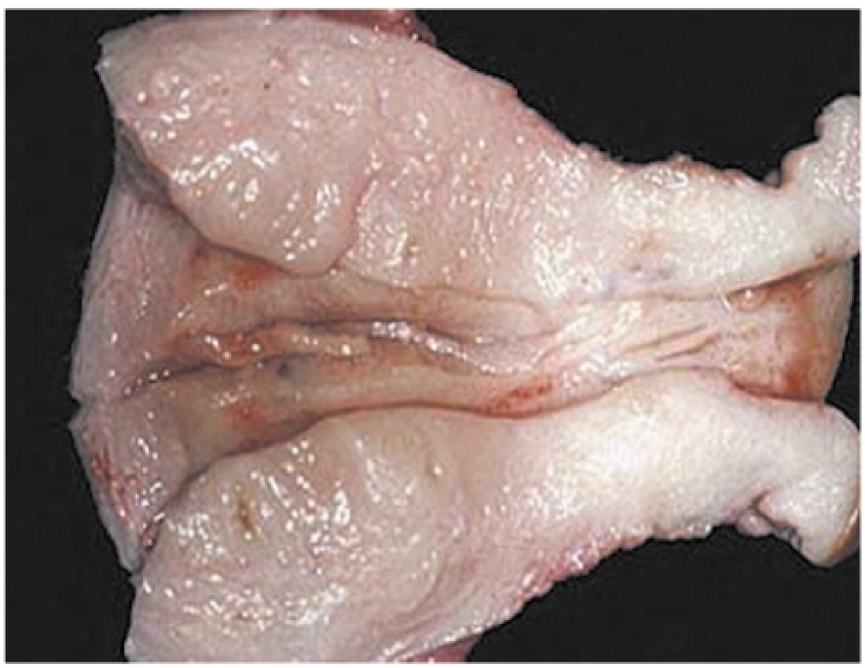
The diagnosis is usually based on histologic findings in surgical specimens, although either form may be suspected clinically. Accordingly, reported incidences in hysterectomy specimens vary depending on the histologic criteria as well as the degree of sectioning, but ranges from 20 to 60 percent (Bird, 1972; Parazzini, 1997).

PATHOPHYSIOLOGY

Anatomy

On gross examination, there typically is global uterine enlargement, but this rarely exceeds that of a 12-week pregnancy. The surface contour is smooth and regular, uterine texture is softened, and reddish myometrial discoloration is common. The grossly cut uterine surface typically appears spongy with focal areas of hemorrhage (Fig. 9-9).

FIGURE 9-9



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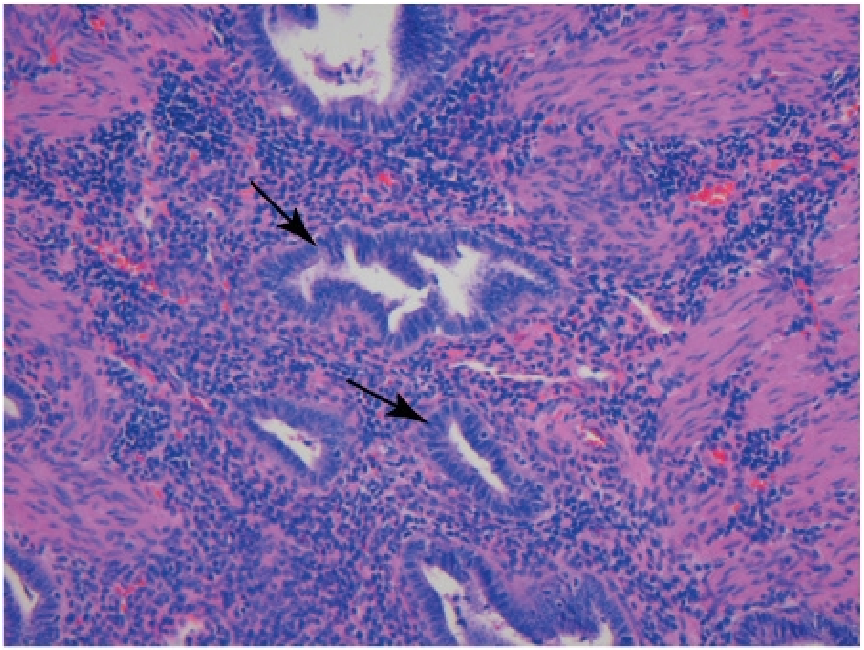
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



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Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Adenomyosis. **A.** Gross bivalved uterine specimen. Note the spongy texture of this uterus with adenomyosis. **B.** Microscopically benign endometrial glands (**arrows**) and stroma infiltrate deeply into the myometrium. *(Courtesy of Dr. Raheela Ashfaq.)*

The ectopic foci of glands and stroma that are found in the myometrium in adenomyosis originate from the basalis layer. Because cells from the basalis layer do not undergo the typical proliferative and secretory changes during the menstrual cycle, hemorrhage within these foci is minimal.

Pathogenesis

The most widely held theory regarding adenomyosis development describes the downward invagination of the endometrial basalis layer deeply into the myometrium. The endometrial-myometrial interface is unique from most mucosal-muscular interfaces in that it lacks an intervening submucosa. Accordingly, even in normal uteri, the endometrium commonly invades the myometrium superficially.

Mechanisms which incite deep myometrial invasion are not known but in some cases, there is myometrial weakness caused by prior pregnancy or surgery or by decreased immunologic activity at the endometrial-myometrial interface (Ferenczy, 1998; Levgur, 2000). Estrogen and progesterone likely play a role in its development and maintenance. For example, adenomyosis develops during the reproductive years and regresses after menopause. Regardless of the permissive cause, cell migration and invasion proceed, and there is degradation and reconstruction of the extracellular matrix.

An alternative theory is that adenomyosis is caused by metaplasia of pluripotent mÃ¼llerian tissue. This theory provides explanation for endometrial rests that have been identified in the rectovaginal septum, far from the uterine endometrium and myometrium (Donnez, 1995).

RISK FACTORS

Parity and age are significant risk factors for adenomyosis. Specifically, nearly 90 percent of cases are in parous women and nearly 80 percent develop in women in their forties and fifties (Lee, 1984).

Adenomyosis is associated with other pathologies that are affected by cytochrome P450 aromatase expression and higher tissue

estrogen levels. These include leiomyomas, endometriosis, and endometrial cancer (Azziz, 1989). As discussed in Chapter 10, however, endometriosis has markedly different epidemiologic characteristics and is thought to arise from another mechanism. Oral contraceptives are not associated with adenomyosis, however, adenomyosis is found more commonly in women taking the selective estrogen receptor modulator tamoxifen (Cohen, 1997; Parazzini, 1997).

SYMPTOMS

About one third of women with adenomyosis have symptoms. Their severity correlates with increasing number of ectopic foci and extent of invasion (Levgur, 2000; Nishida, 1991; Sammour, 2002). Menorrhagia and dysmenorrhea are common. Menorrhagia possibly results from increased and abnormal vascularization of the endometrial lining. Dysmenorrhea is thought to be caused by increased prostaglandin production found in adenomyotic tissues compared with normal myometrium (Koike, 1992). Perhaps 10 percent complain of dyspareunia. Because adenomyosis typically develops in older parous women in their 40s and 50s, infertility is not a common complaint (Nikkanen, 1980).

DIFFERENTIAL DIAGNOSIS

Symptoms may mimic those from leiomyomas, endometrial cancer, endometriosis, and chronic pelvic inflammatory disease. Endometrial cancer, myometrial hypertrophy, or uterine contractions may appear similar to diffuse adenomyosis on sonographic imaging. Focal adenomyosis may share sonographic characteristics of leiomyomas.

DIAGNOSIS

Cancer Antigen 125

For many years, the diagnosis of adenomyosis in most cases has been made retrospectively following hysterectomy. Serum levels of the tumor marker CA125 have been evaluated as a diagnostic tool but have not proven to be helpful. Although CA125 levels are typically elevated in women with adenomyosis, they may also be elevated in those with leiomyomas, endometriosis, pelvic infection, and pelvic malignancies.

Sonography

Because transabdominal sonography does not consistently identify the often subtle myometrial changes of adenomyosis, imaging with TVS is preferred, and MR imaging may be complimentary (Bazot, 2001; Reinhold, 1998).

In the hands of experienced sonographers, findings of diffuse adenomyosis may include: (1) the anterior or posterior myometrial wall appearing thicker than its counterpart, (2) myometrial heterogeneity, (3) small myometrial hypoechoic cysts, representing cystic glands within ectopic endometrial foci, and (4) linear striated projections extending from the endometrium into the myometrium (Reinhold, 1999).

Focal adenomyosis appears as discrete hypoechoic nodules that may be differentiated from leiomyoma by their poorly defined margins, elliptical rather than globular shape, minimal mass effect on surrounding tissues, lack of calcifications, and presence of anechoic cysts of varying diameter (Fedele, 1992; Reinhold, 1998).

Because these findings may be subtle, operator experience influences diagnostic accuracy more than with most other pelvic pathology. Moreover, the presence of other concurrent uterine disease such as leiomyoma or endometrial cancer also limits accuracy. In these settings, MR imaging has proved highly accurate for diagnosis (see Fig. 2-26).

MANAGEMENT

Medical Treatment

Conservative therapy for symptomatic adenomyosis is similar to that for primary menorrhagia or dysmenorrhea. First, NSAIDs are often given (Fraser, 1986; Marjoribanks, 2003). Combination oral contraceptives and progestin-only regimens can be used to induce endometrial atrophy and decrease endometrial prostaglandin production to improve dysmenorrhea and menorrhagia. The levonorgestrel-containing intrauterine system has also been shown to be effective for treatment of adenomyosis (Fedele, 1997).

Because adenomyosis and endometriosis share endometrial origins, some have used GnRH agonists or danazol to treat adenomyosis in a fashion similar to the treatment of endometriosis. There have been no clinical trials, however, to study this

practice.

Interventional Treatment

Hysterectomy is the definitive treatment and as with other conditions, the type of surgical procedure depends on uterine size and associated uterine or abdominopelvic pathology.

Endometrial ablation or resection using hysteroscopy has been used to successfully treat dysmenorrhea and menorrhagia caused by adenomyosis (Molnar, 1997; Wortman, 2000). However, complete eradication of deep adenomyosis is problematic and is responsible for a significant number of treatment failures. Because of this, McCausland and McCausland (1996) recommended preoperative sonography or MR imaging to identify deep lesions, which allows better patient selection. Another caveat is that any injury to the endometrial lining, including ablation, may be the initiating insult that incites endometrial tissue to grow into the myometrium, thus *causing* adenomyosis.

Uterine artery embolization (Uterine Artery Embolization) has also been used to relieve symptoms for some women, although success rates vary widely and range from 25 to 90 percent (Jha, 2003; Kim, 2004; 2007; Toh, 2003).

Myometrial Hypertrophy

In some women, especially those with high parity, there is global enlargement of the uterus but no associated underlying identifiable pathology in hysterectomy specimens (Fraser, 1987). Also known as gravid hypertrophy, this condition results from myometrial fiber enlargement and not hyperplasia or interstitial fibrosis (Traiman, 1996). One definition includes uterine weights exceeding 120 g for nulliparas and 210 g for multiparas (Zaloudek, 2002). Symptoms are uncommon but may include menstrual irregularities, and of these menorrhagia is the most frequent complaint.

Uterine or Cervical Diverticula

These rare ballooned sacculations from the uterine or cervical wall communicate with and extend out from the endometrial cavity or endocervical canal. Many develop after cesarean delivery and are thought to arise at sites of uterine dehiscence. Others are thought to be congenital anomalies developing from a localized duplication of the distal mÃ¼llerian duct on one side (Engel, 1984).

A diverticulum may serve as a passive repository for menstrual flow, with intermittent expulsion of blood producing pain and intermenstrual bleeding. In addition, these saccules may become secondarily infected (Umezaki, 2004).

Transvaginal sonography or sonohysterography are typically used to evaluate women with these symptoms. Hysterosalpingography, hysteroscopy, and MR imaging have been used to show communication to the endometrium (Erickson, 1999). Treatment includes excision of the diverticulum or hysterectomy.

OVARY

Ovarian masses are a common finding in general gynecology. Of these, neoplasms constitute a significant number, and most are benign. Ovarian neoplasms can be distinguished histologically and are grouped as *surface epithelial tumors, germ cell tumors,* and *sex cord-stromal tumors* depending on their cell type of origin (see Fig. 36-1). The types and particular characteristics of these tumors are discussed in Chapters 35 and 36.

Despite continuous improvement in diagnostic methods, it is often impossible to clinically differentiate between benign and malignant conditions. Thus, management must balance concerns of performing an operation for an innocent lesion with the risk of not removing an ovarian malignancy.

Cystic Ovarian Masses

Most benign and malignant ovarian masses are predominantly cystic. The incidence of ovarian cysts varies only slightly with patient demographics and ranges from 5 to 15 percent (Dorum, 2005; Millar, 1993; Porcu, 1994).

Histologically, they are often divided into those derived from neoplastic growth, *ovarian cystic neoplasms* , and those created by disruption of normal ovulation, *functional ovarian cysts* . Differentiation of these is not always clinically apparent using either imaging tools or tumor markers. Accordingly, ovarian cysts are often managed as a single composite clinical entity.

These cysts often require excision because of symptoms or the possibility of cancer, and consequently their economic impact is significant. In their review of indications for hospitalization in the United States, Velebil and colleagues (1995) reported that approximately 200,000 women are admitted annually for benign ovarian cysts, comprising a third of admissions for gynecologic disease.

PATHOGENESIS

The exact mechanisms leading to cyst formation are unclear. Angiogenesis is an essential component of both the follicular and luteal phases of the ovarian cycle. It also participates in various pathologic ovarian processes, including follicular cyst formation, polycystic ovarian syndrome, ovarian hyperstimulation syndrome, and benign and malignant ovarian neoplasms. There is evidence that vascular endothelial growth factor serves as a major mediator of angiogenesis, and it factors into the development of ovarian neoplasms (Abulafia, 2000; Fasciani, 2001; Yamanoto, 1997).

SYMPTOMS

Most women with ovarian cysts are asymptomatic. If symptoms develop, pain and vague pressure sensations are common. Cyclic pain with menstruation may indicate endometriosis and an associated endometrioma (see Chap. 10, Patient Symptoms). Intermittent pain may reflect early torsion, whereas acute severe pain may indicate torsion with resulting ovarian ischemia (Ovarian Remnant Syndrome). Other causes of acute pain include cyst rupture or tubo-ovarian abscess (see Chap. 3, Chronic Pelvic Inflammatory Disease). In contrast, vague pressure or achiness may be the only symptom and can result from stretching of the ovarian capsule. In advanced ovarian malignancies, women complain of increased abdominal girth and early satiety from ascites or an enlarged ovary.

In some women, evidence of hormonal disruption may be found. For example, excess estrogen production from granulosa cell stimulation may disrupt normal menstruation or initiate bleeding in prepubertal or postmenopausal patients (see Chap. 36, Clinical Findings). Similarly, virilization may result from increased androgens produced by theca cell stimulation.

DIAGNOSIS

Many ovarian cysts are asymptomatic and found incidentally on routine pelvic examination or during imaging studies for another indication. Findings may vary, but typically masses are mobile, cystic, nontender, and found lateral to the uterus.

Human Chorionic Gonadotropin

In the evaluation of adnexal pathology, serologic β-hCG testing provides valuable information. Detection of serum β-hCG may indicate ectopic pregnancy or a corpus luteum of pregnancy. Less commonly, β-hCG can also serve as a tumor marker in defining ovarian neoplasm.

Tumor Markers

Tumor markers are typically proteins that are produced by tumor cells or by the body in response to tumor cells. Several such markers have been used to identify ovarian malignancies.

Cancer antigen 125 (CA125) is an antigenic determinant on a high-molecular-weight glycoprotein. As a tumor marker, serum levels are often elevated in women with epithelial ovarian cancer (Menon, 1999). Unfortunately, CA125 is not a tumor-specific antigen, and it is elevated in up to 1 percent of healthy controls. It may also be elevated in women with nonmalignant disease such as leiomyomas, endometriosis, and salpingitis. Despite these limitations, serum CA125 determinations may be helpful and are often used in the evaluation of ovarian cysts.

Serum alpha-fetoprotein (AFP) levels may be elevated in those rare patients with an endodermal sinus tumor or embryonal cell carcinoma. Increased serum levels of β-hCG may indicate an ovarian choriocarcinoma, a mixed germ cell tumor, or embryonal cell carcinoma. Lactate dehydrogenase levels may be increased in those with dysgerminoma, whereas elevated carcinoembryonic antigen and cancer antigen 19-9 (CA 19-9) levels arise from secretions of mucinous epithelial ovarian carcinomas (Campo, 1999). A more detailed discussion of these tumor markers is found in Chapters 36, Laboratory Testing.

Imaging

Both transvaginal sonography (TVS) and transabdominal sonography (TAS) are excellent methods, and cyst size is the main determinant in selecting between the two. For lesions confined to the true pelvis, TVS has superior resolution, whereas TAS is more useful for large tumors (Marret, 2001). Characteristic findings for specific types of ovarian cysts have been described and have also been defined to discriminate malignant from benign lesions (Table 9-4) (Granberg, 1989; Minaretzis, 1994; Okugawa, 2001).

Table 9-4 Recommended Management of Ovarian Masses Found with Imaging

Type of Ovarian Mass	**Recommendation**
Simple Cyst Â± Hemorrhage	
Premenopausal woman	
• ≤3 cm diameter	Invariably functional; no additional treatment required
• >3 cm diameter	The majority are functional; TVS repeated in 6â€“8 weeks;cyst may be removed if persistent
Postmenopausal woman	
• ≤5 cm diameter	The majority are benign; CA125 measurement and repeat TVS recommended; may observe if normal CA125 levelsand no interval cyst growth
• >5 cm diameter	Ovary may be removed if persistent or symptomatic
Complex mass	
Displays any of the following features: ▪ Septation ▪ Mural nodule ▪ Irregular wall thickening ▪ Shadowing echodensity ▪ Regional, diffuse, bright echoes ▪ Hyperechoic lines and dots	Malignancy difficult to exclude unless typical features of mature cystic teratoma or endometrioma identified In postmenopausal women complex masses are removed; in premenopausal women persistent complex masses are removed
Solid or predominantly solid-appearing mass	Recommend removal

CA125 = cancer antigen 125; TVS = transvaginal sonography.

Adapted from Dill-Macky, 2000, with permission.

Traditional gray-scale sonography may also be augmented with color flow Doppler. Transvaginal color Doppler sonography (TV-CDS) may add information regarding the nature of the lesion, its malignant potential, and the presence of torsion (Emoto, 1997; Rosado, 1992; Wu, 1994). For assessing simple ovarian cysts and the risk of malignancy, however, TV-CDS typically adds no significant advantage compared with conventional TVS (Vuento, 1995).

Use of MR imaging for ovarian cyst evaluation has been investigated. Although its added value compared with sonography is limited in most clinical settings, MR imaging may add information in situations in which anatomy or patient habitus complicates sonographic imaging (Outwater, 1996).

MANAGEMENT

Observation

Most ovarian cysts are functional, and most spontaneously regress within 6 months of identification. High-dose oral contraceptive pills have been used by some to hasten cyst resolution, however, Turan and associates (1994) found no additional benefit to this adjunctive therapy.

For postmenopausal women with a *simple* ovarian cyst, expectant management may also be reasonable. A number of investigators have confirmed the safety of this approach when several criteria are met: (1) sonographic evidence of a thin-walled, unilocular cyst; (2) cyst diameter less than 5 cm; (3) no cyst enlargement during surveillance; and (4) normal serum CA125 levels (Menon, 1999; Nardo, 2003).

Surgical Excision

Despite efforts by investigators to classify lesions by radiologic and serologic means, there is considerable morphologic similarity among cyst types as well as between those that are malignant and benign. Accordingly, for many cases, surgical excision of the cyst serves as the definitive diagnostic tool.

Cystectomy versus Oophorectomy

The decision for one surgical technique in preference over the other is dictated by lesion size, age, and intraoperative findings. For example, in premenopausal women, smaller lesions generally require only cystectomy with preservation of reproductive function. Larger lesions may necessitate oophorectomy because of the difficulty with cyst enucleation without rupture and the greater risk of malignancy in these larger cysts. However, in postmenopausal women, oophorectomy is preferred because the risk for cancer is higher and benefits to ovarian salvage are limited (Okugawa, 2001).

Clinical findings of malignancy at the time of surgery will dictate further actions. Multiple small lesions studding the peritoneal surface, ascites, and exophytic growths extending from the ovarian capsule should prompt appropriate clinical staging and treatment for ovarian cancer as discussed in Chapter 35, Management of Early-Stage Ovarian Cancer.

Laparoscopy

The surgical approach for cyst excision is also dictated by clinical factors. Laparoscopy has many advantages, but it generally has been underused for management of ovarian cysts. Concerns of increased rates of cyst rupture with the risk for tumor spill and malignant seeding have caused many to avoid this modality. That said, several investigators have documented the safety of laparoscopic cystectomy and oophorectomy (Lin, 1995; Mais, 1995; Yuen, 1997).

Mini-Laparotomy

For small or moderately sized cysts, laparotomy incisions can usually be minimized. As a result, most who undergo mini-laparotomy can be discharged the day of surgery (Berger, 1994; Flynn, 1999). Although mini-laparotomy typically offers shorter operative times, lower rates of cyst rupture, and greater cost savings compared with laparoscopy or laparotomy, this approach can limit lysis of adhesions and inspection of peritoneal surfaces for signs of ovarian malignancy.

Laparotomy

Women with a greater potential for malignancy are best managed by laparotomy, as it provides a surgical field large enough for oophorectomy or cyst enucleation without tumor rupture or spill and for surgical staging if malignancy is found.

Cyst Aspiration

Historically, there has been hesitation to aspirate ovarian cysts because of possible intraperitoneal seeding by early stage ovarian cancer. Moreover, nondiagnostic, false-positive, and false-negative results are common (Dejmek, 2003; Martinez-Onsurbe, 2001; Moran, 1993). For these reasons, very few indications exist for this procedure.

Role of the Generalist

Ovarian cysts frequently require surgical treatment. Most of these lesions are benign and typically are removed by general gynecologists. When malignancy is present, however, formal cancer staging should accompany excision. Studies support that

optimal surgical resection and proper staging performed by gynecologic oncologists during the primary operation for ovarian cancers are major factors in long-term survival. Thus, women with pelvic masses and preoperative findings suspicious for malignancy are generally referred. The American College of Obstetricians and Gynecologists and Society of Gynecologic Oncologists (2002) have presented guidelines regarding clinical criteria that should prompt referral to a gynecologic oncologist (Table 9-5). If one or more criteria from this list or other suspicious findings are identified, referral should follow (Im, 2005).

Table 9-5 Guidelines for Referral of Newly Diagnosed Pelvic Mass to Gynecologic Oncologist
Premenopausal woman (<50 years) ■ CA125 >200 U/mL ■ Ascites ■ Evidence of abdominal or distant metastasis (by examination or imaging study) ■ Family history of breast or ovarian cancer (in a first-degree relative)
Postmenopausal woman (≥50 years) ■ CA125 >35 U/mL ■ Ascites ■ Nodular or fixed pelvic mass ■ Evidence of abdominal or distant metastasis (by examination or imaging study) ■ Family history of breast or ovarian cancer (in a first-degree relative)

Data from the American College of Obstetricians and Gynecologists, 2002, with permission.

Functional Ovarian Cysts

Of the different type of ovarian cysts, functional ovarian cysts are common. They originate from follicles and are created by hormonal dysfunction related to ovulation. They are subcategorized as either *follicular cysts* or *corpus luteum cysts* based on both their pathogenesis and histologic qualities. They are not neoplasms and derive mass from accumulation of intrafollicular fluids rather than cellular proliferation. Hormonal dysfunction prior to ovulation results in expansion of the follicular antrum with serous fluid and formation of a follicular cyst. In contrast, following ovulation excessive hemorrhage may fill the corpus luteum, creating corpus luteum cysts. Although these cysts generally have similar symptoms and management, they differ in the potential hormones produced as well as histologic appearance.

RISK FACTORS

Smoking

Several epidemiologic studies have linked smoking with functional cyst development (Holt, 2005; Wyshak, 1988). Although the exact mechanism(s) by which cigarette smoking exerts its effect is not known, changes in gonadotropin secretion and ovarian function are suspected (Michnovicz, 1986; Zumoff, 1990).

Contraception

High-dose oral hormonal contraceptives suppress ovarian activity and protect against cyst development (Ory, 1974). Subsequent studies, however, have shown only modest protective effects from low-dose monophasic or low-dose triphasic contraceptives (Chiaffarino, 1998; Holt, 2003).

By contrast, there is an increased incidence of follicular cysts reported with many progestin-only contraceptives. Recall that continuous, low-dose progestins do not completely suppress ovarian function (see Chap. 5, Oral Progestins). As a result, dominant follicles may develop in response to gonadotropin secretion, yet the normal ovulatory process is frequently disrupted. Follicles fail

to rupture and follicular cysts develop. In clinical studies, cystic masses were found on bimanual pelvic examination in 2 to 9 percent of women using the progestin-only implants (Brache, 2002). Similarly, levonorgestrel-containing intrauterine devices have been associated with the development of functional ovarian cysts (Inki, 2002).

One intriguing observation is that bilateral tubal ligation has been associated with an increased risk of these cysts (de Alba, 2000; Holt, 2003). The mechanism for this is unclear.

Tamoxifen

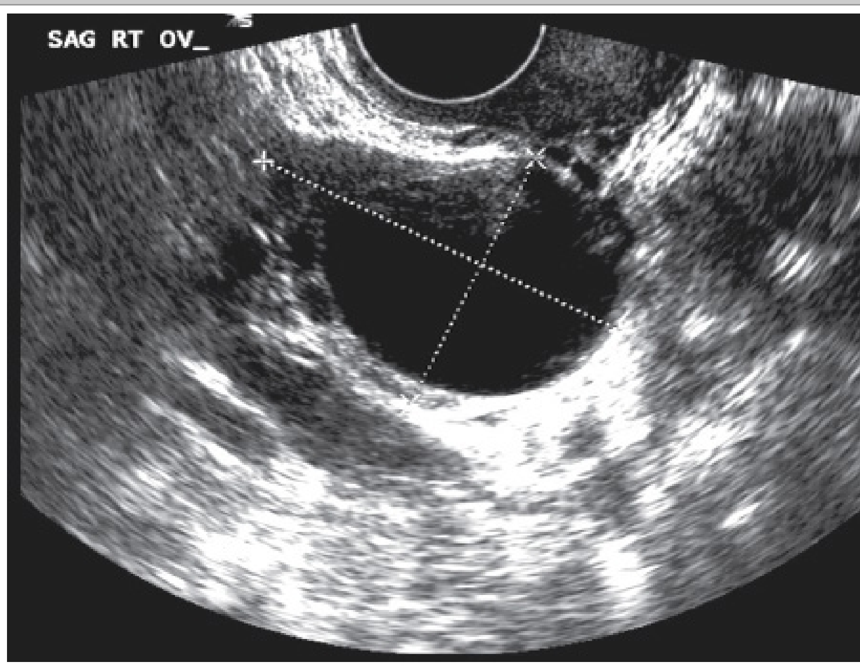
Women treated with tamoxifen for breast cancerâ€”either pre- or postmenopausalâ€”have an increased risk for ovarian cyst formation. Most studies report rates of 15 to 30 percent compared with 7 percent cited for the general postmenopausal population (Cohen, 2003; Mourits, 1999). Premenopausal women are disparately affected, and from 30 to 80 percent of women in this age group develop cysts (Mourits, 1999; Shushan, 1996).

Most of these are believed to be functional cysts, but the exact mechanism by which tamoxifen stimulates their formation is unknown. Fortunately, the majority of these cysts resolve with time whether tamoxifen treatment is continued or discontinued (Lindahl, 1997; Shushan, 1996). If small simple cysts are found, these women should undergo sonographic surveillance. However, if clinical signs of malignancy are present (see Table 9-5), then surgical exploration is indicated and tamoxifen use is discontinued.

DIAGNOSIS AND TREATMENT

Functional cysts are managed similarly to other cystic ovarian lesions. Consequently, sonography is the imaging tool of choice for evaluation. Typically, follicular cysts are completely rounded anechoic lesions with thin, regular walls (Fig. 9-10).

FIGURE 9-10



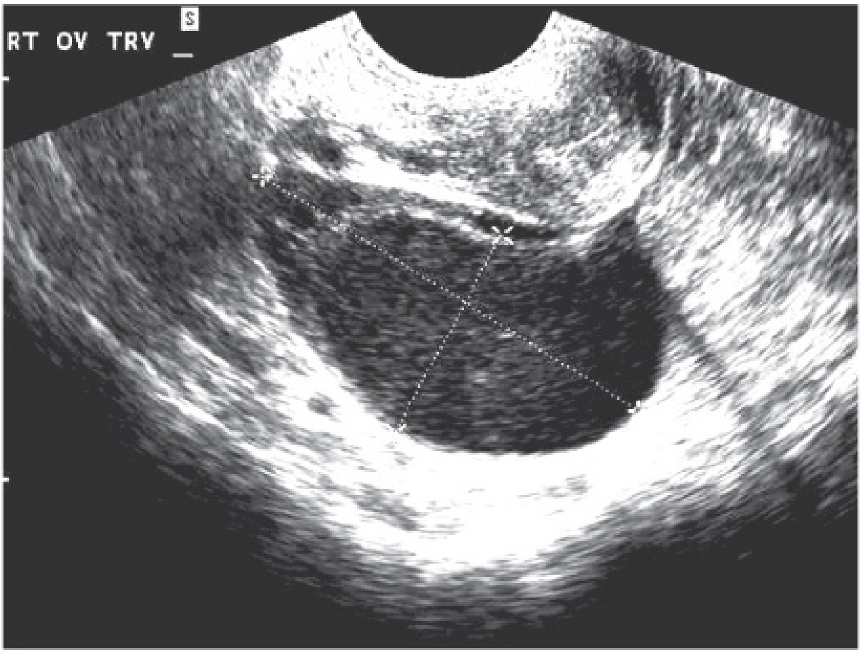
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Transvaginal sonogram of an ovary containing a follicular cyst. Note the smooth walls and lack of internal echoes. *(Courtesy of Dr. Elysia Moschos.)*

Conversely, corpus luteum cysts are termed "great imitators" because of their varied sonographic characteristics (Fig. 9-11). Immediately following hemorrhage into its cavity, the cyst generally appears echogenic and mimics a solid mass. With evolution of

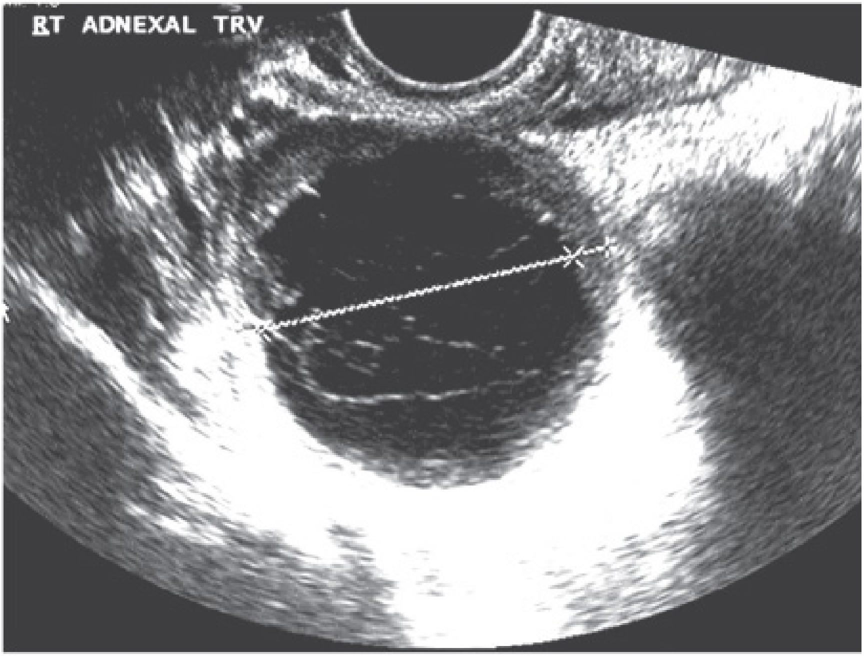
the clot, a lacy reticular pattern develops. As the clot hemolyzes, a distinct line often forms between the serum and retracting clot. With further retraction, the clot may appear as an intramural nodule. Imaging with transvaginal color Doppler typically displays a brightly colored ring because of their increased surrounding vascularity (Swire, 2004; Yoffe, 1991). This *ring of fire* is also common to ectopic pregnancies (see Fig. 7-7).

FIGURE 9-11



A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Transvaginal sonogram of a hemorrhagic corpus luteum cyst. **A.** Diffuse low level echoes, which are commonly associated with hemorrhage, are seen throughout this smooth-walled cyst. **B.** Reticular interfaces are another commonly demonstrated sonographic finding within a resolving hemorrhagic cyst. *(Courtesy of Dr. Elysia Moschos.)*

If asymptomatic, women with findings of functional ovarian cyst may be observed, but surgical evaluation is often required for persistent cysts.

Benign Neoplastic Ovarian Cysts

These lesions, in combination with functional ovarian cysts, comprise the majority of ovarian masses. Of benign ovarian neoplasms, serous and mucinous cystadenomas (surface epithelial neoplasia group) and mature cystic teratomas (germ cell family) are by far the most common (Pantoja, 1957b). Qualities of the surface epithelial neoplasia group are discussed further in Chapter 35, whereas mature cystic teratoma are discussed below.

OVARIAN TERATOMA

These belong to the germ cell family of ovarian neoplasms. Teratomas arise from a single germ cell, and therefore may contain any of the three germ layersâ€”ectoderm, mesoderm, or endoderm. These layers typically form tissues that are foreign to the ovary and that have a disorganized structure. As a result, teratomas usually contain a haphazard collection of tissues such as hair, fat, bone, and teeth. The term "dermoid" was later coined to describe mature cystic teratomas, because of the prevalence of dermal elements in these cysts.

Teratomas are classified as:

- Immature teratomaâ€”This neoplasm is malignant. Immature tissues from one, two, or all three germ cell layers are found and frequently coexist with mature elements. These tumors are discussed in greater detail in Chapter 36, Immature Teratomas.
- Mature teratomaâ€—This benign tumor contains mature forms of the three germ cell layers and are categorized as:

(1) Mature cystic teratomas, which develop into cystic structures and may be known by several names, including *mature cystic teratoma, benign cystic teratoma,* and *dermoid cyst;*

(2) Mature solid teratomas, which have elements formed into a solid mass;

(3) Fetiform teratomas or homunculus, which forms a doll-shape and arranges the germ cell layers with considerable normal spatial differentiation;

(4) Monodermal teratoma, which is composed either solely or predominantly of only one highly specialized tissue type. Of the monodermal teratomas, those composed dominantly of thyroid tissue are termed *struma ovarii* .

Mature Cystic Teratoma (Benign Cystic Teratoma or Dermoid Cyst)

These common tumors comprise approximately 10 to 25 percent of all ovarian neoplasms and 60 percent of all benign ovarian neoplasms (Katsube, 1982; Koonings, 1989; Peterson, 1955).

Pathology

The typically sturdy cyst walls of mature cystic teratomas give these cysts a smooth, rounded or ovoid shape and lobulation is uncommon. These cystic tumors are typically slow growing and most measure between 5 and 10 cm (Comerci, 1994; Pantoja, 1975a). They are bilateral in approximately 10 percent of cases (Caruso, 1971; Katsube, 1982; Peterson, 1955).

When sectioned, most cysts appear unilocular and typically contain one area of localized growth that protrudes into the cystic cavity. Alternatively designated as *Rokitansky protuberance, dermoid plug, dermoid process, dermoid mamilla,* or *embryonal rudiment,* this protuberance may occasionally be absent or multiple.

Microscopically, endodermal or mesodermal derivatives may be found, but ectodermal elements usually predominate. The cyst is typically lined with keratinized squamous epithelium and contains abundant sebaceous and sweat glands. Hair and fatty secretions are commonly found within (Figs. 9-12 and 9-13). The Rokitansky protuberance is usually where the most varied tissue types are found and is also a common site of malignant transformation.

FIGURE 9-12

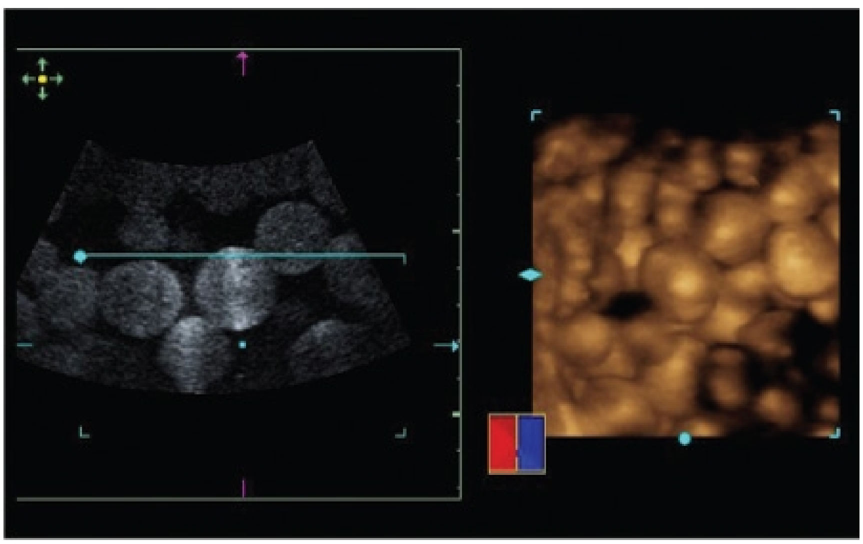
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Gross photograph of an opened mature cystic teratoma. Hair and sebum are prominent in this tumor.

FIGURE 9-13

A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Mature cystic teratoma. **A.** This unique presentation of mature cystic teratoma contains multiple symmetric balls of sebum and squames. Hair and fluid are intermixed. **B.** Two-dimensional and three-dimensional transvaginal sonograms of the same cyst. *(Courtesy of Dr. Patricia Santiago-Munoz and Lesly Sherman, RDMS.)*

Malignant transformation develops in only 1 to 3 percent of cases, typically in women older than 40, and these cancers comprise only 1 percent of all ovarian malignancies (Kelley, 1961; Koonings, 1989; Peterson, 1957). Because of the preponderance of

squamous epithelium lining these cysts, it seems logical that squamous cell carcinoma comprises 80 percent of malignant cases.

Tumor Origin

The diverse tissues found within teratomas are thought not to arise by fertilization of an egg by sperm. Instead, they are theorized to develop from genetic material contained within a single oocyte. Complete embryonic development from asexual reproductionâ€”*parthenogenesis* â€”is found in lower phylogenetic organisms. In mammals, the process falls short of normal embryogenesis, but some embryonic tissue development may occur. It appears that oocytes capable of parthenogenesis result from an arrest of oocyte development following meiosis I (Eppig, 1977; Linder, 1975). As a result, almost all mature cystic teratomas have a 46, XX karyotype.

Complications

Almost 15 percent of mature cystic teratomas undergo torsion, but cyst rupture is rare. Presumably, their thick cyst wall resists rupture compared with other ovarian neoplasms. If cysts do rupture, acute peritonitis is common, and Fielder and associates (1996) attribute peritonitis to the sebum and hair contents of these cysts. They showed the benefits of lavage to prevent peritonitis and adhesion formation. Alternatively, chronic leakage of teratoma contents can lead to a granulomatous peritonitis that may initially be visually misinterpreted as widespread malignancy (Phupong, 2004).

Risk Factors

Mature cystic teratomas are found in women from childhood to after menopause. In their review of nearly 1,000 cases, Peterson and co-workers (1955) found 91 percent of tumors in women aged 15 to 50 years with a peak incidence in those 20 to 40 years (Benjapibal, 2000; Comerci, 1994).

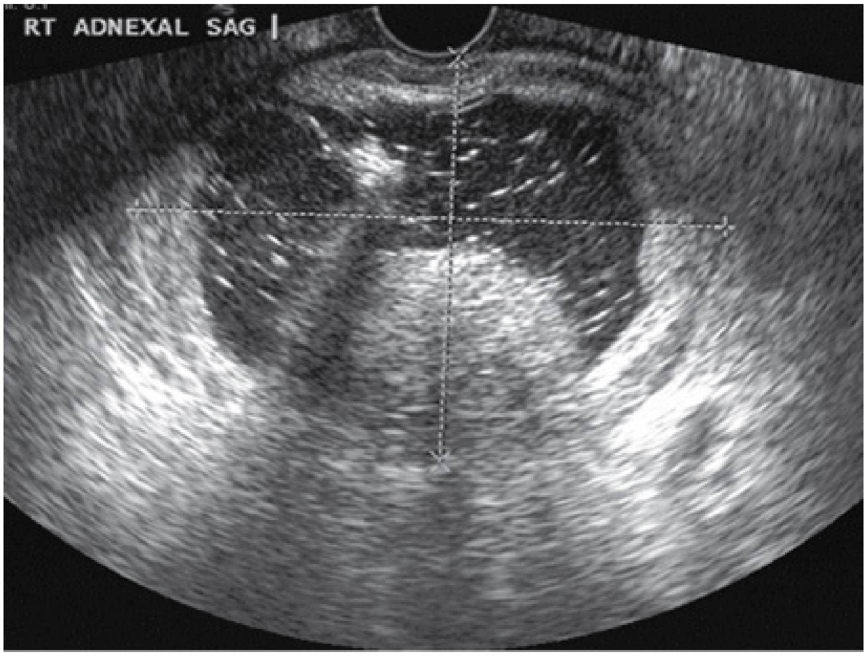
These tumors are frequently identified during pregnancy. Although cause and effect seems unlikely, up to 10 percent of mature cystic teratomas are diagnosed in pregnant women. These account for one fourth to one half of ovarian tumors diagnosed at that time (Sherard, 2005; Usui, 2000).

Diagnosis

Symptoms from mature cystic teratomas are similar to those of other ovarian cysts. As a result, sonography is the main imaging tool used in their identification (Fig. 9-14). As described earlier, these tumors have a wide range of consistencies, from completely cystic to completely solid. Despite these variations, mature cystic teratomasâ€”more so than most ovarian tumorsâ€”display a number of characteristic sonographic features:

- "Tip of the iceberg"â€”This sign is created by amorphous echogenic interfaces of fat, hair, and tissues in focus in the foreground that shadow and thus obscure structures behind it (Guttman, 1977).
- Fat-fluid or hair-fluid levelsâ€”A distinct linear demarcation can be seen within the cyst when serous fluid interfaces with sebum alone or sebum mixed with hair.
- Hairâ€—This frequent component of mature cystic teratomas, when intermixed with sebum, forms accentuated lines and dots that represent hair in longitudinal and transverse planes (Bronshtein, 1991).
- Rokitansky protuberanceâ€—This mural nodule found in the majority of mature teratomas has a characteristic sonographic appearance. The typically rounded protuberance ranges in size from 1 to 4 cm, is predominantly hyperechoic, and creates an acute angle with the cyst wall.

FIGURE 9-14



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Sonogram revealing characteristics of mature cystic teratoma. White dashes are hair and a large mural nodule is seen along the lower cyst wall. *(Courtesy of Dr. Elysia Moschos.)*

Although these findings are frequently seen in mature cystic teratomas, they may also be found in other ovarian cysts. For example, Patel and associates (1998) reported modest positive predictive values for these findings individually. However, they described values of 100 percent when two or more were found within a given lesion.

Treatment

For most women with mature cystic teratoma, surgical excision provides a definitive diagnosis, affords relief of symptoms, and prevents complications of torsion, rupture, and malignant degeneration. As with other ovarian cysts, excision may be by laparoscopic or laparotomic approach, and either cystectomy or oophorectomy can be performed. Cystectomy offers comparable clinical success to oophorectomy for women who wish to preserve fertility. Mais and co-workers (2003) identified no recurrences in women undergoing cystectomy for a mature cystic teratoma by either laparoscopy or laparotomy.

In the past, most recommended that the opposite ovary be explored because of the high frequency of bilateral lesions. Surgeons commonly bivalved, wedged, or biopsied grossly normal contralateral ovaries. With accurate sonographic imaging, these procedures are no longer indicated with a normal appearing contralateral ovary (Comerci, 1994).

Solid Ovarian Tumors

Completely solid ovarian masses typically are benign. That said, these masses should still be removed because of the inability to exclude malignancy in these tumors. Ovarian tumors may presents as a solid mass and may represent sex cord-stromal tumors, Krukenberg tumor, ovarian leiomyoma and leiomyosarcoma, carcinoid, primary lymphoma, and transition cell tumors, also called Brenner tumors.

Ovarian Remnant Syndrome

Persistent functional ovarian tissue following incomplete oophorectomy can present as a pelvic mass if ovarian pathology develops.

In symptomatic women, they most commonly cause pain and are discussed in detail in Chapter 11, Ovarian Remnant Syndrome and Ovarian Retention Syndrome (Mahdavi, 2004). Dense adhesive disease at the time of oophorectomy is the greatest risk factor, and women with a history of pelvic inflammatory disease, endometriosis, or pelvic surgery are more commonly affected (Nezhat, 2005).

TORSION OF ADNEXAL MASSES

Torsion involves the twisting of adnexal components. Most commonly, the ovary and fallopian tube rotate as a single entity around the broad ligament. Infrequently, the ovary may alone turn about its mesovarium, and rarely the fallopian tube may twist alone about the mesosalpinx (Lee, 1967). Torsion may occur with normal adnexa, but in 50 to 80 percent of cases unilateral ovarian masses are identified (Nichols, 1985; Warner, 1985).

Incidence

Adnexal torsion is most common during the reproductive years. Hibbard and colleagues (1985) found that 70 percent of cases developed in women aged 20 to 39 years. Postmenopausal women may also be affected. A disproportionate number of cases of adnexal torsion develop during pregnancy, and these compose 20 to 25 percent of all torsion cases.

Pathophysiology

Adnexal masses with increased mobility have greater torsion rates. Congenitally long ovarian ligaments create excessively mobile mesovaria or fallopian tubes and may increase the risk in even normal adnexa (Bellah, 1989; Graif, 1988). Similarly, pathologically enlarged ovaries with a diameter more than 6 cm will typically arise from the true pelvis. Without these bony confines, mobility and risk of torsion are increased. Accordingly, the highest rates of torsion are found in adnexal masses from 6 to 10 cm (Houry, 2001). Masses that are lighter relative to their radius are also at increased risk.

Two key points assist in initially maintaining blood flow to the involved adnexal structures despite twisting of their vascular pedicles. First, adnexa are supplied from the adnexal branches of both the uterine and ovarian vessels. During torsion, one of these, but not the other, may be involved. Secondly, although low-pressure veins draining the adnexa are compressed by the twisting pedicle, high-pressure arteries initially resist compression. During torsion, as a result of this continued inflow but arrested egress of blood, the adnexa become congested and edematous, but do not infarct. Because of this, it is reasonable to conservatively manage cases of early torsion. With continued stromal swelling, however, arteries may become compressed, leading to infarction and necrosis.

Symptoms

Classically, a woman with adnexal torsion complains of sharp lower abdominal. The onset is sudden and worsens intermittently over several hours. The pain usually is localized to the involved side, with radiation to the flank and thigh. Low-grade fever suggests adnexal necrosis. Nausea and vomiting frequently accompany the pain.

Diagnosis

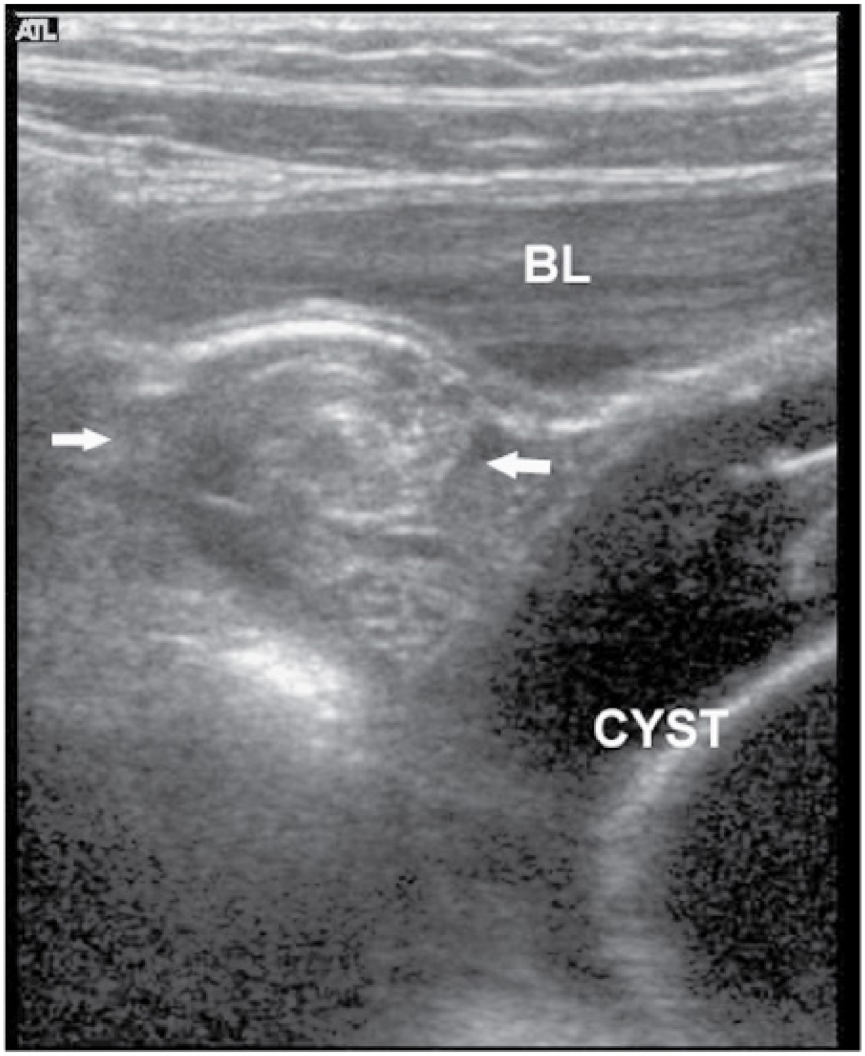
IMAGING

Sonography plays an essential role in evaluation. Sonographic findings, however, can vary widely depending on the degree of vascular compromise, the characteristics of any associated intraovarian or intratubal pathology mass, and the presence or absence of adnexal hemorrhage. Sonographically, torsion may mimic ectopic pregnancy, tubo-ovarian abscess, hemorrhagic ovarian cyst, and endometrioma. Accordingly, rates of correct diagnosis with sonography range from 50 to 75 percent (Graif, 1984; Helvie, 1989).

Despite these limitations, specific findings associated with ovarian torsion have been described. First, the presence of multiple follicles rimming an enlarged ovary has a reported detection rate of 64 percent (Farrell, 1982; Graif, 1988). This finding reflects ovarian congestion and edema described earlier. As shown in Figure 9-15, the twisted pedicle may also give the appearance described as a bull's-eye target, a whirlpool, or a snail shell, that is, a rounded hyperechoic structure with multiple inner concentric hypoechoic broad rings (Vijayaraghavan, 2004). Transvaginal color Doppler sonography (TV-CDS) may add significant information

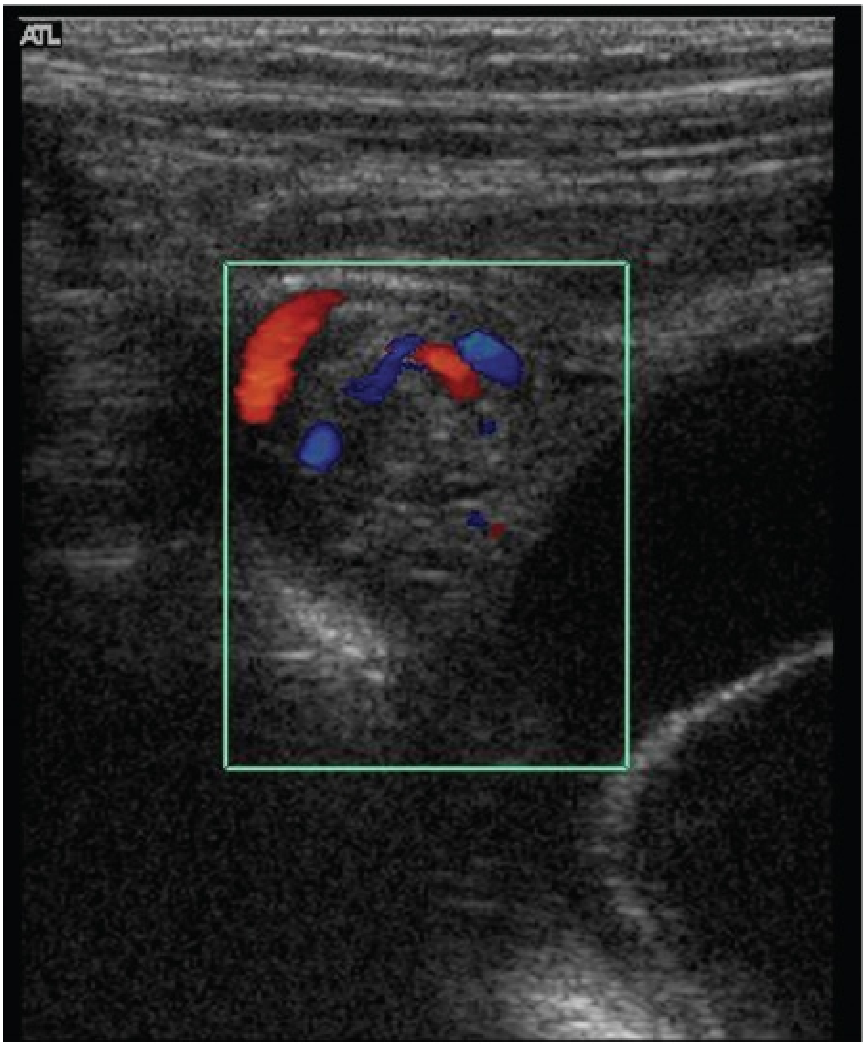
for clinical evaluation. Commonly, disruption of normal adnexal blood flow can be seen (Albayram, 2001). In most cases, intraovarian venous flow is absent. As torsion advances, intraovarian arterial flow may subsequently be lacking. However, despite its typical high predictive value for most cases, adnexa with incomplete or intermittent torsion may at times still display both venous and arterial flow. Thus, disruption of vascular flow is highly suggestive of torsion, but torsion should not be excluded on the basis of a normal Doppler study alone.

FIGURE 9-15



A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Whirlpool sign of ovarian torsion seen with transvaginal sonography. **A.** Conventional transabdominal sonography. White arrows point to torsion of ovarian vessels. A portion of large ovarian cyst (CYST) involved with the torsion is seen to the right of the twisted ovarian vessels. BL = bladder. **B.** Transvaginal color Doppler shows twisting of the vessels. *(Vijayaraghavan, 2004, with permission.)*

Computed tomography or MR imaging may be helpful in complicated cases, or in those with ambiguous clinical presentation such as that seen with incomplete or chronic torsion (Rha, 2002).

Management

Salvage of the involved adnexa, resection of any associated cyst or tumor, and possible oophoropexy are goals of treatment. Findings of adnexal necrosis or rupture with hemorrhage, however, may necessitate removal of torsed structures.

Torsion may be evaluated by laparoscopy or laparotomy techniques. Previously, when surgical exploration was performed, adnexectomy was usually done to avoid possible thrombus release upon detorsion and subsequent embolism. Evidence does not support this. McGovern and co-workers (1999) reviewed nearly 1,000 cases of torsion and found pulmonary embolism in only 0.2 percent. Of note, these cases of embolism were associated with adnexal excision and none were linked to conservative untwisting of the pedicle. In a study of 94 women with adnexal torsion, Zweizig and associates (1993) reported no increased morbidity in

women undergoing untwisting of the adnexa compared with those undergoing adnexectomy.

For these reasons, detorsion of the adnexa is generally recommended. Within minutes following untwisting, congestion is relieved, and ovarian cyanosis and volume typically diminish. For many, absence of these changes may prompt adnexal removal. A persistently black-bluish ovary, however, is not pathognomonic for necrosis, and the ovary may still recover. Cohen and associates (1999) reviewed 54 cases in which adnexa were preserved regardless of their appearance following detorsion. They reported functional integrity and successful subsequent pregnancy in almost 95 percent. Bider and colleagues (1991) observed no increased postoperative infectious morbidity in cases similarly managed. Because necrosis may still occur, conservative management necessitates postoperative vigilance for fever, leukocytosis, and peritoneal signs.

Specific ovarian lesions should be excised. Cystectomy in an ischemic, edematous ovary, however, may technically be difficult. Therefore, some authors recommend delaying cystectomy until 6 to 8 weeks after primary intervention (Rody, 2002).

Following detorsion, there is no consensus as to the management of the adnexa. As conservative management has evolved, the incidence of repeated torsion will likely increase. Unilateral or bilateral oophoropexy has been described to minimize the risk of repeat ipsilateral torsion or contralateral adnexal torsion (Djavadian, 2004; Germain, 1996).

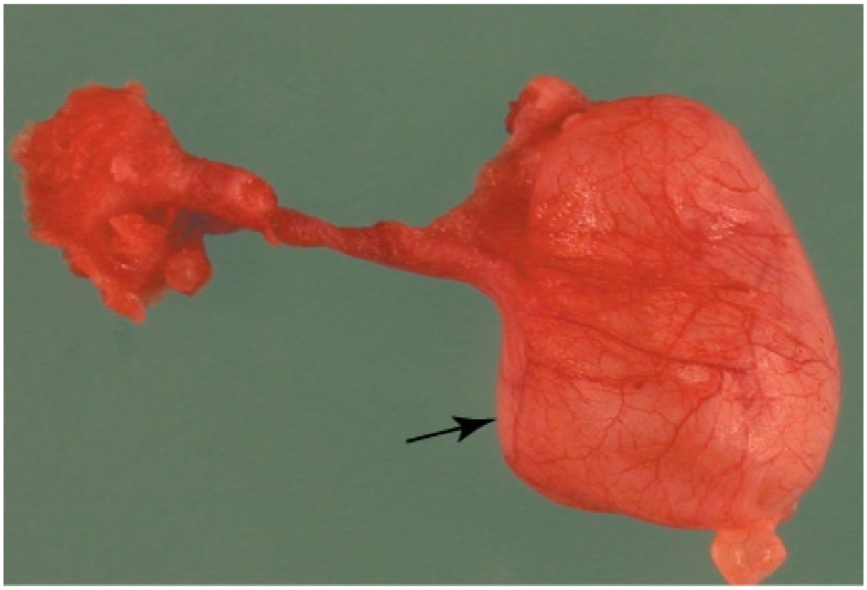
Management during pregnancy does not differ. If the corpus luteum is removed before 10 weeks' gestation, intramuscular 17-hydroxyprogesterone caproate, 150 mg, is recommended to maintain pregnancy. If between 8 and 10 weeks, then only one injection is required immediately after surgery. If the corpus luteum is excised between 6 to 8 weeks, then two additional doses should be given 1 and 2 weeks after the first.

PARAOVARIAN MASSES

Paraovarian and Paratubal Cysts

These arise as either embryologic remnants or as true neoplasms. Most paraovarian cysts are not neoplastic, but are either distended remnants of the mesonephric ducts or mesothelial inclusion cysts (see Fig. 18-1). Extremes of size have been noted but most measure less than 3 cm (Genadry, 1977). The most common paratubal cyst is the *hydatid of Morgagni* , which is pedunculated and typically dangles from one of the fimbria (Fig. 9-16). Neoplastic paraovarian cysts are rare, and histologically resemble tumors of ovarian origin. They are usually cystadenomas or cystadenofibromas and are rarely of borderline potential or malignant (Honore, 1980; Korbin, 1998).

FIGURE 9-16



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Surgical specimen of a paratubal cyst (**arrow**) attached to a small tubal segment. This pedunculated and thin walled nature of these cysts is typical. *(Courtesy of Dr. Raheela Ashfaq.)*

The reported incidence of para-adnexal cysts varies, but a recent autopsy series cited a rate of about 5 percent of adnexal cysts (Dorum, 2005). No certain risks have been associated with their formation, although some have reported them to be more common following in-utero exposure to diethylstilbestrol (Haney, 1986; Wise, 2005a).

Para-adnexal cysts are most commonly identified in asymptomatic women at the time of surgery or sonography for other gynecologic problems. They are generally not detected on pelvic examination. If symptoms develop, they mimic those of any other ovarian pathology such as abdominal or pelvic pain or increasing girth. They are infrequently associated with complications such as hemorrhage, rupture, or torsion (Genadry, 1977).

Transvaginal sonography is often used as the primary tool for evaluation of a symptomatic woman. Most cysts have thin, smooth walls and anechoic centers. Eccentrically located cysts may resemble hydrosalpinx. Sonography, however, has limitations in differentiating between paraovarian and ovarian pathology (Athey, 1985; Barloon, 1996). Moreover, MR imaging was not found helpful in differentiating between ovarian and paraovarian cysts (Ghossain, 2005). Thus, many women are managed similarly as for the diagnosis of ovarian cyst. When surgically managed, cystectomy, or less frequently drainage and fulguration of the cyst wall, are performed.

Paraovarian Solid Tumors

Leiomyoma is the most common solid paraovarian mass, with pathophysiology identical to those within the myometrium. Infrequently, congenital anomalies such as an accessory or supernumerary ovary or a rudimentary uterine horn may be present. Other rare paraovarian solid tumors include sarcomas, lymphoma, adenocarcinoma, pheochromocytoma, choriocarcinoma, and solid Wolfiian duct remnants.

Most paraovarian solid tumors are asymptomatic and identified on routine pelvic examination. Occasionally, there is unilateral pelvic or abdominal pain. Sonography and MR imaging are used to visualize these masses, although accurate differentiation between benign and malignant lesions is typically not possible. Thus, most solid masses are surgically removed.

FALLOPIAN TUBE PATHOLOGY

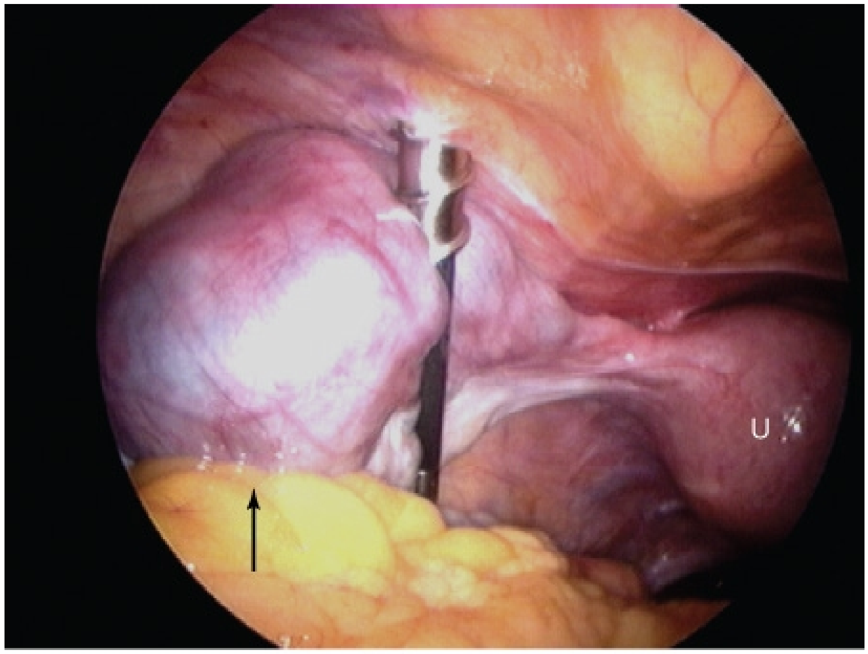
The bulk tubal pathologies involve ectopic pregnancy (see Chap 7) or the sequelae of pelvic inflammatory disease (PID) (see Chap.

3, Pelvic Inflammatory Disease). Fallopian tube neoplasms are rare (see Chap. 35, Fallopian Tube Carcinoma).

Hydrosalpinx

This chronic swelling of the fallopian tube is commonly a long-term result of PID. Accordingly, risk factors are the same as those for PID. Grossly, the fine fimbria and tubal ostia are obliterated and replaced by a smooth, clubbed end (Fig. 9-17). The ballooned, thin walls of the elongated tube are whitish and translucent, and the tube is typically distended with a clear serous fluid. Depending on the degree and location of the ipsilateral ovary, the hydrosalpinx may be adhered to it.

FIGURE 9-17



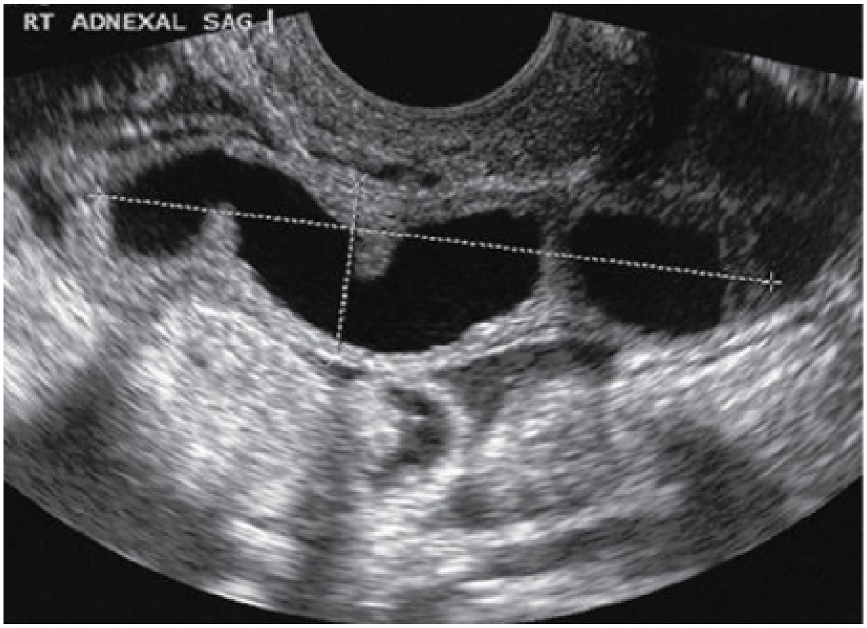
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Laparoscopic photograph of hydrosalpinx. Note the thin-walled balloon fallopian tube and its clubbed fimbriated end. *(Courtesy of Dr. Kevin Doody.)*

Hydrosalpinx may be found in asymptomatic women during pelvic examination or sonography done for other indications. Some women note infertility or chronic pelvic pain. The differential diagnosis mimics that for other cystic pelvic lesions discussed on Cystic Ovarian Masses. In general, no laboratory test is helpful, and serum CA125 level testing for presumed ovarian malignancy is typically negative.

Sonography has low sensitivity for detection of hydrosalpinges during infertility evaluation. However, in women with sonographic findings, there is usually a thin-walled, hypoechoic cystic structure with incomplete septa (Fig. 9-18). In some, multiple hyperechoic mural nodules measuring 2 to 3 mm arch around the inner circumference of the tube to create the *beads on a string* sign. These nodules represent fibrotic endosalpingeal folds.

FIGURE 9-18



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Transvaginal sonogram of hydrosalpinx. An incomplete septum, which is a fold of the dilated tube, is seen within this fusiform, fluid-filled structure. *(Courtesy of Dr. Elysia Moschos.)*

Management varies depending on the conviction of diagnosis, desire for future fertility, and associated symptoms. In asymptomatic women who have completed childbearing, and in whom the sonographic evidence supports the diagnosis of hydrosalpinx, expectant management is typical. In those with pelvic pain, infertility, or in whom the diagnosis is uncertain, diagnostic laparoscopy is performed.

For women not wishing to preserve fertility, laparoscopic treatment may include lysis of adhesions and salpingectomy. Conversely, in women who desire fertility, surgical intervention depends on the degree of tubal damage (see Chap. 20, Correction of Anatomic Abnormalities). As the degree of tubal distortion increases, fertility rates decrease (Schlaff, 1990). In women with mild tubal disease, laparoscopic neosalpingostomy has resulted in 80-percent pregnancy rates and is a reasonable approach. In those women with severe disease, in vitro fertilization (IVF) may offer a greater chance at fertility.

Of note, women with a hydrosalpinx who undergo IVF have about half the pregnancy rate of other women (American Society for Reproductive Medicine, 2004b). One theoretical explanation is that the hydrosalpinx fluid bathes the endometrial cavity with toxic fluid that contains bacteriologic agents, debris, lymphocytes, cytokines, lymphokines, and prostaglandins. This is suggested to lower blastocyst implantation and affect embryo growth (Johnson, 2004; Strandell, 2002). This is supported by studies showing improved subsequent pregnancy, implantation, and live birth rates following resection of hydrosalpinges prior to IVF (Dechaud, 1998; Johnson, 2004; Strandell, 1999). For all of these reasons, the American Society for Reproductive Medicine (2004b) recommends such surgery prior to IVF.

Benign Neoplasms

These tumors of the fallopian tube are rare. For example, the most common benign tumor of the fallopian tube is the mesothelioma, which is found in less than 1 percent of specimens (Pauerstein, 1968). Previously termed adenomatoid tumors, these 1- to 2-cm, well-circumscribed solid nodules arise in the tubal wall (Salazar, 1972). Tubal leiomyomas are uncommon and derive from the smooth muscle of the muscularis, broad ligament, or from vessels in either location. Additionally, hemangioma,

lipoma, chondroma, adenofibroma, cystadenofibroma, angiomyolipoma, and neural tumors may rarely develop.

Tubo-Ovarian Abscess

Tubo-ovarian abscess (TOA) is usually a consequence of pelvic inflammatory disease (PID). Occasionally, however, endometritis, pyelonephritis, and pelvic malignancy may be the source. Pelvic abscesses are classically polymicrobial with predominance of anaerobic bacteria. Infrequently in the United States, TOA may follow *Actinomyces* infection complicating use of an intrauterine device (see Chap. 5, Infection), or pelvic tuberculosis may form TOAs (Chow, 2002; Fiorino, 1996).

Women with TOA most commonly present with lower abdominal pain and with unilateral or bilateral adnexal masses. Fever and leukocytosis may be absent. Abscess rupture causes severe pain with chills, fever, and progressive peritonitis. If large volumes of pus are released into the peritoneal cavity, infection may spread upward along the colonic gutters to form subphrenic abscesses that cause shoulder pain. Sonography is typically diagnostic, but surgical exploration may be required to confirm the diagnosis. Tubo-ovarian abscess is more fully discussed in Chapter 3, Sonography.

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ENDOMETRIOSIS: INTRODUCTION

Endometriosis is a common benign gynecologic disorder defined as the presence of endometrial glands and stroma outside of the normal location. First identified in the mid-nineteenth century (Von Rokitansky, 1860), endometriosis is most commonly found on the pelvic peritoneum but may also be found on the ovaries, rectovaginal septum, ureter, and rarely in the bladder, pericardium, and pleura (Comiter, 2002; Giudice, 2004). Endometriosis is a hormonally dependent disease and as a result is chiefly found in reproductive-aged women. Endometrial tissue located within the myometrium is termed adenomyosis and is discussed in greater detail in Chapter 9, Adenomyosis.

The incidence of endometriosis is difficult to quantify, as women with the disease are often asymptomatic, and imaging modalities have low sensitivities for diagnosis. Women with endometriosis may be asymptomatic, subfertile, or suffer varying degrees of pelvic pain. The primary method of diagnosis is laparoscopy, with or without biopsy for histologic diagnosis (Kennedy, 2005; Marchino, 2005). Using this standard, investigators have reported the annual incidence of surgically diagnosed endometriosis to be 1.6 cases per 1,000 women aged between 15 and 49 years (Houston, 1987). In asymptomatic women, the prevalence of endometriosis ranges from 2 to 22 percent, depending on the population studied (Eskenazi, 1997; Mahmood, 1991; Moen, 1997). However, because of its link with infertility and pelvic pain, endometriosis is notably more prevalent in subpopulations of women with these complaints. In infertile women, the prevalence has been reported to be between 20 to 50 percent and in those with pelvic pain, 40 to 50 percent (Balasch, 1996; Eskenazi, 2001).

PATHOPHYSIOLOGY

Etiology

Although the definitive cause of endometriosis remains unknown, several theories with supporting evidence have been described.

RETROGRADE MENSTRUATION

The earliest and most widely accepted theory relates to retrograde menstruation through the fallopian tubes with subsequent dissemination of endometrial tissue within the peritoneal cavity (Sampson, 1927). Refluxed endometrial fragments adhere to and invade the peritoneal mesothelium and develop a blood supply, which leads to continued implant survival and growth (Giudice, 2004).

First proposed in the 1920s, this theory has gained support with the findings of greater volumes of refluxed blood and endometrial tissue in the pelves of women with endometriosis (Halme, 1984). Uterine hyperperistalsis and dysperistalsis have been noted in women with endometriosis and resulted in subsequent increased endometrial reflux (Leyendecker, 2004). Additionally, D'Hooghe (1997) demonstrated that surgical obliteration of the cervical outflow tract in baboons leads to the induction of endometriosis. Women with amenorrhea due to outflow tract obstruction similarly have a high incidence of endometriosis, which is often relieved by correction of the obstruction (Sanfilippo, 1986).

LYMPHATIC OR VASCULAR SPREAD

Evidence also supports the concept of endometriosis originating from aberrant lymphatic or vascular spread of endometrial tissue (Ueki, 1991). Findings of endometriosis in unusual locations, such as the perineum or groin, bolster this theory (Mitchell, 1991; Pollack, 1990). The retroperitoneal region has abundant lymphatic circulation. Thus, cases in which no peritoneal implants are found, but solely isolated retroperitoneal lesions are noted, suggest lymphatic spread (Moore, 1988). Additionally, the tendency of

endometrial adenocarcinoma to spread via the lymphatic route indicates the ease at which endometrium can be transported by this route (McMeekin, 2003). Although this theory remains attractive, few studies have experimentally evaluated this form of endometriosis transmission.

COELOMIC METAPLASIA

The theory of coelomic metaplasia suggests that the parietal peritoneum is a pluripotential tissue that can undergo metaplastic transformation to tissue histologically indistinguishable from normal endometrium. Because the ovary and the progenitor of the endometrium, the mÃ¼llerian ducts, are both derived from coelomic epithelium, metaplasia may explain the development of ovarian endometriosis. In addition, the theory has been extended to include the peritoneum because of the proliferative and differentiation potential of the peritoneal mesothelium. This theory is attractive in instances of endometriosis in the absence of menstruation, such as in premenarchal and postmenopausal women, and in males treated with estrogen and orchiectomy for prostatic carcinoma (Dictor, 1988; Pinkert, 1979). However, the absence of endometriosis in other tissues derived from coelomic epithelium argues against this theory.

INDUCTION THEORY

Finally, the induction theory proposes that some hormonal or biologic factor(s) may induce the differentiation of undifferentiated cells into endometrial tissue (Vinatier, 2001). These substances may be exogenous or released directly from the endometrium (Bontis, 1997). In vitro studies have demonstrated the potential for ovarian surface epithelium, in response to estrogens, to undergo transformation to form endometriotic lesions (Matsuura, 1999). Although many putative factors have been identified, their propensity to cause endometriosis in some women but not in others demonstrates the still unidentified etiology of this disease.

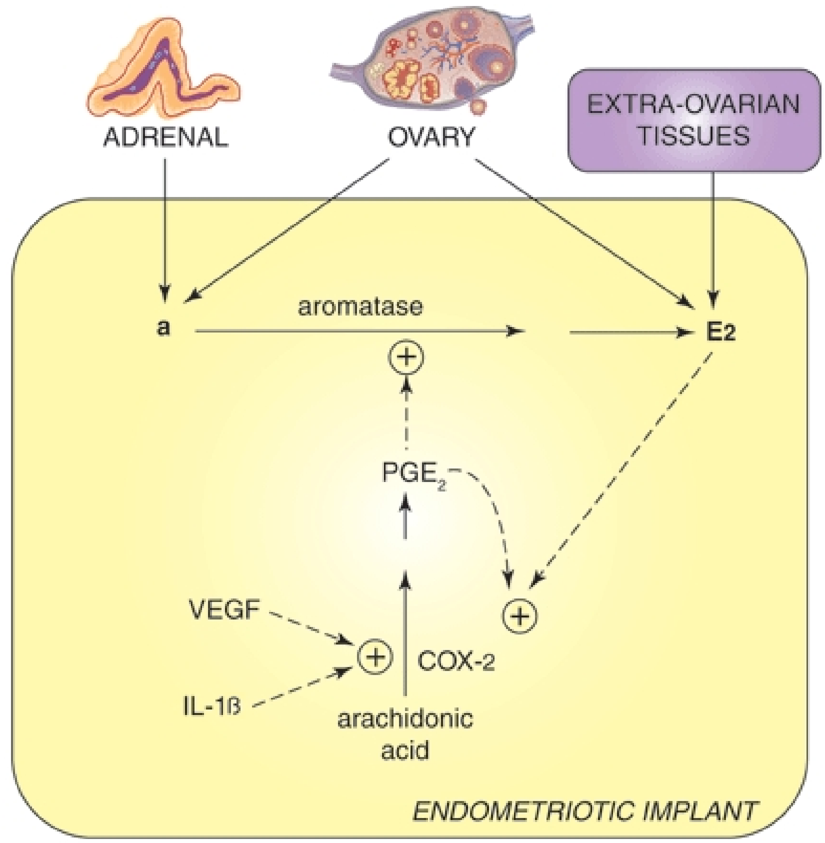
Hormonal Dependence

One factor that has been definitively established as having a causative role in the development of endometriosis is estrogen (Gurates, 2003). Although most estrogen in women is produced directly by the ovaries, numerous peripheral tissues are also known to create estrogens through aromatization of ovarian and adrenal androgens. Endometriotic implants have been shown to express aromatase and 17β-hydroxysteroid dehydrogenase type 1, the enzymes responsible for conversion of androstenedione to estrone and of estrone to estradiol, respectively. Implants, however, are deficient in 17β-hydroxysteroid dehydrogenase type 2, which inactivates estrogen (Kitawaki, 1997; Zeitoun, 1998). This enzymatic combination ensures that implants will be exposed to an estrogenic environment. Furthermore, the locally produced estrogens within endometriotic lesions may exert their biologic effect within the same tissue or cell in which they are produced, a process referred to as *intracrinology* .

In contrast, normal endometrium does not express aromatase and has elevated levels of 17β-hydroxysteroid dehydrogenase type 2 in response to progesterone, which ensures that estrogenic effects are attenuated in response to progesterone (Satyaswaroop, 1982). As a result, progesterone antagonizes the estrogen effects in normal endometrium during the luteal phase of the menstrual cycle. Endometriosis, however, manifests a relative progesterone-resistant state, which prevents attenuation of the estrogen stimulation in this tissue (Attia, 2000).

Prostaglandin E_2 (PGE_2) is the most potent inducer of aromatase activity in endometrial stromal cells, acting through the prostaglandin EP_2 receptor subtype (Noble, 1997; Zeitoun, 1999). Estradiol produced in response to the increased aromatase activity subsequently augments PGE_2 production by stimulating cyclooxygenase type 2 (COX-2) enzyme in uterine endothelial cells (Fig. 10-1) (Bulun, 2002; Gurates, 2003). This creates a positive feedback loop and potentiates the estrogenic effects on proliferation of endometriosis. This concept of locally produced estrogens and intracrine estrogen action in endometriosis serves as the basis for pharmacologic inhibition of aromatase activity in cases of endometriosis that are refractory to standard therapy.

FIGURE 10-1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Activation of COX-2 in endometrial stromal cells results in upregulation of PGE_2 , a potent stimulator of aromatase in endometrial stromal cells. Aromatase activity results in intracellular aromatization of androgens to increase intracellular estradiol via an intracrine mechanism. a = androgen; E_2 = estradiol; COX-2 = cyclooxygenase 2; PGE_2 = prostaglandin E2; IL-1β = interleukin 1β; VEGF = vascular endothelial growth factor.

Role of the Immune System

Although most women experience retrograde menstruation, which may play a role in the seeding and establishment of implants, few develop endometriosis. Menstrual tissue and endometrium that is refluxed into the peritoneal cavity is usually cleared by immune cells such as macrophages, natural killer (NK) cells, and lymphocytes. For this reason, immune system dysfunction is one likely mechanism for the genesis of endometriosis in the presence of retrograde menstruation (Seli, 2003). Impaired cellular and humoral immunity and altered growth factor and cytokine signaling have each been identified in endometriotic tissues.

Macrophages act as scavenger cells in various tissues and increased numbers have been found in the peritoneal cavity of women with endometriosis (Haney, 1981; Olive, 1985b). Although this increased population might logically act to suppress endometrial proliferation, macrophages in these women, however, have a stimulatory effect on endometriotic tissue. In one study, circulating monocytes obtained from women with endometriosis enhanced the in vitro proliferation of cultured endometrial cells, whereas the monocytes from women without endometriosis had the opposite effect (Braun, 1994). It appears therefore that impaired function, and not population size, of macrophages allows endometriotic tissue proliferation.

Natural killer cells are immune cells that have cytotoxic activity against foreign cells. Although the number of NK cells is unaltered in the peritoneal fluid of women with endometriosis, decreased NK cell cytotoxicity against endometrium has been demonstrated

(Ho, 1995; Wilson, 1994). Specifically, the peritoneal fluid from women with endometriosis has been found to suppress NK cell activity, suggesting that soluble factors may play a role in NK cell suppression (Oosterlynck, 1993).

Cellular immunity may also be disordered in women with endometriosis, and T lymphocytes are implicated. For example, in women with endometriosis compared with unaffected women, total lymphocyte numbers or helper/suppressor subpopulation ratios do not differ in peripheral blood, but peritoneal fluid lymphocyte numbers are increased (Steele, 1984). Also, the cytotoxic activity of T lymphocytes against autologous endometrium in affected women is impaired (Gleicher, 1984).

Humoral immunity has also been shown to be altered in affected women and is suggested to play a role in the development of endometriosis. Endometrial antibodies of the IgG class are more frequently detected in the serum of women with endometriosis (Odukoya, 1995). One study also identified IgG and IgA autoantibodies against endometrial and ovarian tissues in the sera and in cervical and vaginal secretions of affected women (Mathur, 1982). These results suggest that endometriosis may be, in part, an autoimmune disease. This may explain some of the factors influencing lower pregnancy and in vitro fertilization (IVF) implantation rates in women with endometriosis (Dmowski, 1995).

Cytokines are small, soluble immune factors involved in paracrine and autocrine signaling of other immune cells. Numerous cytokines, especially interleukins, have been implicated in the pathogenesis of endometriosis. Increased levels of interleukin-1β (IL-1β) have been identified in the endometrial fluid of those with endometriosis (Mori, 1991). Moreover, IL-6 has been shown to be increased in endometrial stromal cells of affected women (Tseng, 1996). Accordingly, IL-6 serum levels greater than 2 pg/mL and tumor necrosis factor-α (TNF-α) peritoneal fluid levels more than 15 pg/mL may be used to discriminate between those with or without endometriosis (Bedaiwy, 2002). Similarly, IL-8 peritoneal fluid levels are elevated in affected individuals and stimulate proliferation of endometrial stromal cells (Arici, 1996; Arici, 1998; Ryan, 1995).

Other noninterleukin cytokines and growth factors are associated with the pathogenesis of endometriosis. For example, both monocyte chemoattractant protein-1 (MCP-1) and RANTES (regulated on activation, normal T-cell expressed and secreted) are chemoattractant for monocytes. Levels of these cytokines are increased in the peritoneal fluid of those with endometriosis and positively correlate with disease severity (Arici, 1997; Khorram, 1993). In addition, vascular endothelial growth factor (VEGF) is an angiogenic growth factor, which is upregulated by estradiol in endometrial stromal cells and peritoneal fluid macrophages. Levels of this factor are increased in the peritoneal fluid of affected women (McLaren, 1996). Although the exact role of these cytokines is not clear, perturbations in their expression and activity further support an immunologic role in the pathogenesis of endometriosis.

RISK FACTORS

Familial Clustering

There is evidence of a familial inheritance pattern for endometriosis. Although no apparent mendelian genetics inheritance pattern has been identified, the increased incidence in first-degree relatives suggests a polygenic/multifactorial inheritance pattern. For example in a genetic study of women with endometriosis, Simpson and his colleagues (1980) noted that 5.9 percent of female siblings and 8.1 percent of the mothers of affected women had endometriosis compared with 1 percent of the husband's female first-degree relatives. Further research has revealed that women with endometriosis and an affected first-degree relative were more likely to have severe endometriosis (61%) than women without an affected first-degree relative (24 percent) (Malinak, 1980). Moreover, Stefansson and his associates (2002), in their analysis of a large population-based study in Iceland, demonstrated a higher kinship coefficient in women with endometriosis compared with matched controls. In this study, the risk ratios were 5.2 for sisters and 1.56 for cousins. Studies have also demonstrated concordance for endometriosis in monozygotic twin-pairs, suggesting a familial/genetic basis (Hadfield, 1997; Treloar, 1999).

Genetic Mutations and Polymorphisms

Rates of familial clustering noted above suggest polygenic inheritance and several candidate genes have been investigated. Two approaches to identify genes involved with endometriosis include sibling-pair linkage analysis and high-throughput analysis of gene expression patterns using microarray technology.

The largest study to date, examining over 1,000 affected sister-pair families, has identified a region on chromosome 10q26 that

demonstrates significant linkage in these sisters affected with endometriosis (Treloar, 2005). This study also revealed a smaller linkage on chromosome 20p13. Two candidate genes within or near this locus have been identified. One such gene is *EMX2* , a transcription factor necessary for reproductive tract development. It has been shown to be aberrantly expressed in the endometrium of women with endometriosis (Daftary, 2004). The second gene is *PTEN* , a tumor suppressor gene implicated in the malignant transformation of ovarian endometriosis (Bischoff, 2000). Studies are currently underway to further determine the role of these genes in endometriosis.

Microarray technology has been used to analyze differences in gene expression in eutopic endometrium (endometrium found normally lining the endometrial cavity) from women without endometriosis compared with that from women with endometriosis (Kao, 2003). Researchers found that several genes were differentially regulated in the eutopic endometrium in women with endometriosis. These include those coding for interleukin 15, glycodelin, Dickkopf-1, semaphorin E, aromatase, progesterone receptor, and various angiogenic factors. Although some of these genes have previously been shown to play a role in endometriosis, others have not been implicated until recently, and their role remains to be elucidated.

Several other genes have been identified, through genetic mutations, polymorphisms, or differential gene expression, to be associated with endometriosis. Although investigations have demonstrated polymorphisms of these genes occur with greater frequency in women suffering with endometriosis, their role in disease causation has not been determined. A more thorough review of candidate genes in the epidemiology of endometriosis can be found at the website http://www.well.ox.ac.uk/~krinaz/genepi_endo.htm .

Anatomic Defects

Reproductive outflow tract obstruction can predispose to development of endometriosis, likely through exacerbation of retrograde menstruation (Breech, 1999). Accordingly, endometriosis has been identified in women with noncommunicating uterine horn, imperforate hymen, and transverse vaginal septum (see Chap. 18, Transverse Vaginal Septum) (Schattman, 1995). Because of this association, diagnostic laparoscopy to identify and treat endometriosis is suggested at the time of corrective surgery for many of these anomalies. Repair of such anatomic defects is thought to decrease the risk of developing endometriosis (Joki-Erkkila, 2003; Rock, 1982).

Environmental Toxins

There have been numerous studies suggesting that exposure to environmental toxins may play a role in the development of endometriosis. The toxins most commonly implicated are 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and other dioxin-like compounds (Rier, 2003). In binding, TCDD activates the aryl hydrocarbon receptor. This receptor functions as a basic transcription factor, and similarly to the steroid hormone receptor family of proteins, leads to the transcription of various genes. As a result, TCDD and other dioxin-like compounds may stimulate endometriosis through increases in interleukin levels, activation of cytochrome P-450 enzymes such as aromatase, and alterations in tissue remodeling. Moreover, TCDD in conjunction with estrogen appears to stimulate endometriosis formation, and TCDD appears to block the progesterone-induced regression of endometriosis (Rier, 2003).

In the environment, TCDD and dioxin-like compounds are waste by-products of industrial processing. Ingestion of contaminated foods or accidental contact is the most common method of exposure. Although endometriosis and TCDD were initially linked in primates, human studies also note a higher prevalence of endometriosis in women with high breast milk dioxin concentrations (Koninckx, 1994; Rier, 1993). In addition, subsequent studies have demonstrated higher serum dioxin levels in infertile women with endometriosis compared with those in infertile controls (Mayani, 1997).

CLASSIFICATION AND LOCATION OF ENDOMETRIOSIS

Classification System

The primary method of endometriosis diagnosis is visualization of endometriotic lesions by laparoscopy, with or without histologic confirmation. Since the extent of endometriosis can vary widely between individuals, attempts have been made to develop a standardized classification to objectively assess the extent of endometriosis. The initial classification system attempted to provide a

scoring system to describe the pathologic extent of disease. Initially created by the American Fertility Society (AFS) 1979, which has been subsequently renamed the American Society for Reproductive Medicine (ASRM), this classification system was subsequently revised by the AFS (American Fertility Society, 1985). This revision allowed for a three-dimensional view of endometriosis and differentiated between superficial and invasive disease. Unfortunately, studies revealed that both of these classification systems did not provide any prognostic information with respect to subsequent fertility or severity of pelvic pain (Guzick, 1982, 1997). For example, one study has suggested that pain correlates with depth of invasion, which is not a significant factor in the scoring system (Koninckx, 1991).

In 1996, in an attempt to further correlate surgical findings with clinical outcomes, the ASRM further revised the endometriosis classification system (American Society of Reproductive Medicine, 1997). In this system, endometriosis is classified as stage I (minimal), stage II (mild), stage III (moderate), and stage IV (severe) (Fig. 10-2). Although there was no change in the staging system from the 1985 classification, the revised 1996 classification provided for description of endometriotic lesion morphology as white, red, or black. This modification was prompted by studies demonstrating that some biochemical activities within implants and possibly disease prognosis can be predicted by implant morphology (Vernon, 1986).

FIGURE 10-2

AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE
REVISED CLASSIFICATION OF ENDOMETRIOSIS

Patient's Name ______________ Date ______________

Stage I (Minimal) - 1-5
Stage II (Mild) - 6-15
Stage III (Moderate) - 16-40
Stage IV (Severe) - >40
Total ______________

Laparoscopy ______ Laparotomy ______ Photography ______
Recommended Treatment ______________

Prognosis ______________

	ENDOMETRIOSIS	<1cm	1-3cm	>3cm
PERITONEUM	Superficial	1	2	4
	Deep	2	4	6
OVARY	R Superficial	1	2	4
	Deep	4	16	20
	L Superficial	1	2	4
	Deep	4	16	20

	Partial	Complete
POSTERIOR CULDESAC OBLITERATION	4	40

	ADHESIONS	<1/3 Enclosure	1/3-2/3 Enclosure	>2/3 Enclosure
OVARY	R Filmy	1	2	4
	Dense	4	8	16
	L Filmy	1	2	4
	Dense	4	8	16
TUBE	R Filmy	1	2	4
	Dense	4*	8*	16
	L Filmy	1	2	4
	Dense	4*	8*	16

*If the fimbriated end of the fallopian tube is completely enclosed, change the point assignment to 16.

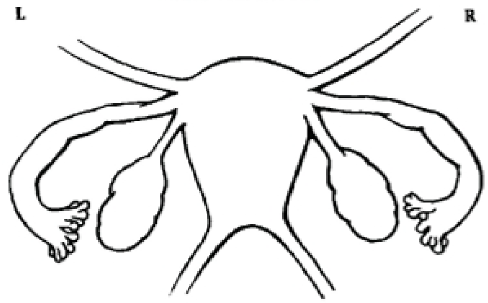
Denote appearance of superficial implant types as red [(R), red, red-pink, flamelike, vesicular blobs, clear vesicles], white [(W), opacifications, peritoneal defects, yellow-brown], or black [(B) black, hemosiderin deposits, blue]. Denote percent of total described as R__% W__% and B__%. Total should equal 100%.

described as R___%, W___% and B___%. Total should equal 100%.

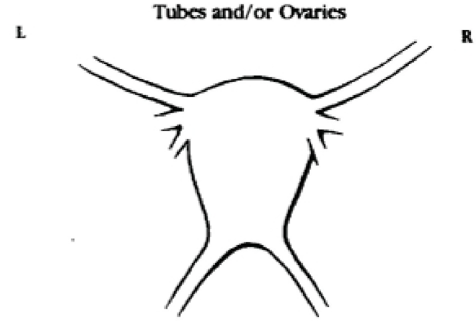
Additional Endometriosis: ______________________

Associated Pathology: ______________________

To Be Used with Normal Tubes and Ovaries



To Be Used with Abnormal Tubes and/or Ovaries



Vol. 67, No. 5, May 1997 American Society for Reproductive Medicine *Revised ASRM classification: 1996*

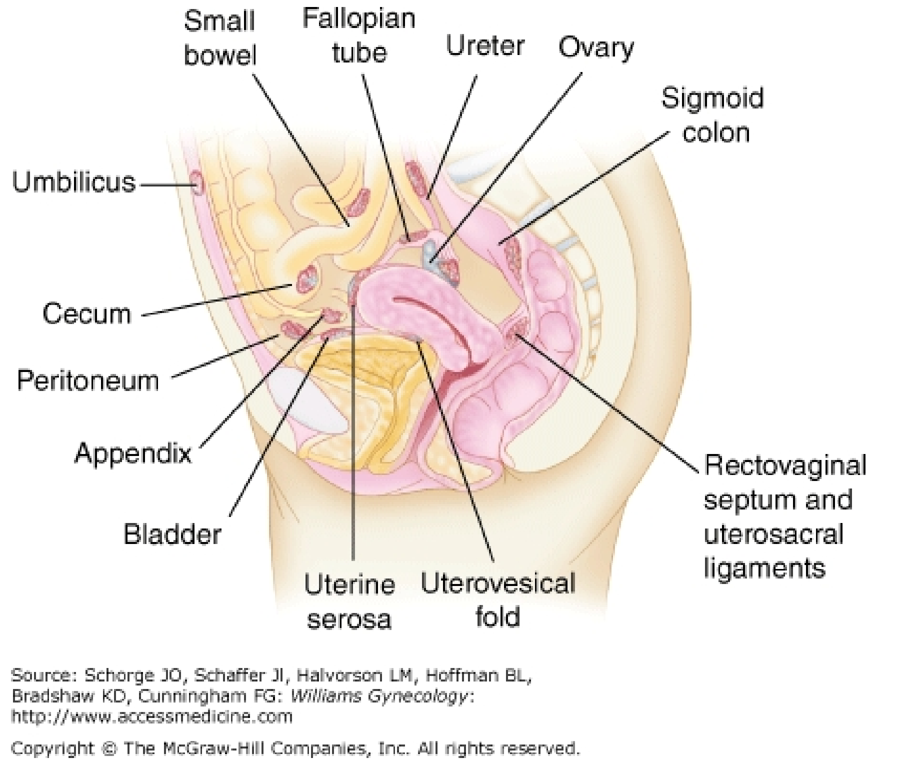
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

American Society for Reproductive Medicine Revised Classification of Endometriosis. Available at: http://www.asrm.org/Literature/classifications/classification_endometriosis.pdf *(From the American Society for Reproductive Medicine, 1997, with permission.)*

Anatomic Sites

Endometriosis may develop anywhere within the pelvis and on other extrapelvic peritoneal surfaces. Most commonly, endometriosis is found in the dependent areas of the pelvis. The ovary, pelvic peritoneum, anterior and posterior cul-de-sac, and uterosacral ligaments are frequently involved (Fig. 10-3). Additionally, the rectovaginal septum, ureter, and rarely the bladder, pericardium, surgical scars, and pleura may be affected. One pathologic review revealed that endometriosis has been identified on all organs except the spleen (Markham, 1989). Rare sites of endometriosis may present with atypical cyclic symptoms. For example, women with urinary tract endometriosis may describe cyclic irritative voiding symptoms and hematuria; those with rectosigmoid involvement may note cyclic rectal bleeding; and pleural lesions have been associated with menstrual pneumothorax or hemoptysis (Price, 1996; Roberts, 2003; Ryu, 2007; Sciume, 2004).

FIGURE 10-3



Common locations of endometriosis within the abdomen and pelvis. *(Redrawn after Olive, 2005.)*

Ovarian endometriomas are a common manifestation of endometriosis. These smooth-walled, dark-brown ovarian cysts are filled with a chocolate-appearing fluid and may be unilocular or when larger, multilocular. Ovarian endometriomas are thought to form through invagination of ovarian cortex and subsequent incorporation of menstrual debris that had been adherent to the ovarian surface (Hughesdon, 1957). Another theory has suggested that endometriomas develop as a result of coelomic metaplasia of invaginated epithelial inclusions (Nisolle, 1997).

PATIENT SYMPTOMS

Although women with endometriosis may be asymptomatic, symptoms are common and typically include chronic pelvic pain and infertility. As previously stated, the current ASRM classification of endometriosis, which describes the extent of disease bulk, poorly predicts symptoms. Thus clinically, women with extensive disease (stage IV) may note few complaints, whereas those with minimal disease (stage I) may have significant pain or subfertility or both.

Pain

Endometriosis is a common cause of pelvic pain, which in affected women can vary greatly and may be cyclic or chronic (Mathias, 1996). The underlying cause of this pain is unclear, but proinflammatory cytokines and prostaglandins released by endometriotic implants into the peritoneal fluid may be one source (Giudice, 2004). Additionally, there is also evidence to suggest that pain from endometriosis correlates with depth of invasion and that the site of pain may indicate lesion location (Chapron, 2003; Koninckx, 1991). Recent data suggest that endometriosis pain may result from neuronal invasion of endometriotic implants that subsequently develop a sensory and sympathetic nerve supply, which may undergo central sensitization (see Chapter 11). (Berkley, 2005). This leads to persistent hyperexcitability of the neurons and subsequent persistent pain, despite surgical excision. Whatever the cause, clinically women with endometriosis experience different manifestations of pain.

DYSMENORRHEA

Cyclic pain with menstruation is noted commonly in women with endometriosis. Typically, endometriosis-associated dysmenorrhea precedes menses by 24 to 48 hours and is less responsive to nonsteroidal anti-inflammatory drugs (NSAIDs) and combination oral contraceptives (COCs). This pain is thought to be more severe in comparison with primary dysmenorrhea, and Cramer and associates (1986) demonstrated a positive correlation between the severity of dysmenorrhea and the risk of endometriosis. Furthermore, deeply infiltrating endometriosis, that is, disease that extends >5 mm under the peritoneal surface, also appears to have positive correlation to the severity of dysmenorrhea (Chapron, 2003).

DYSPAREUNIA

Endometriosis-associated dyspareunia is most often related to rectovaginal septum or uterosacral ligament disease, and is less commonly associated with ovarian involvement (Murphy, 2002; Vercellini, 1996b). During intercourse, tension on diseased uterosacral ligaments may be the trigger of this pain (Fauconnier, 2002). Although some women with endometriosis may describe a history of dyspareunia since coitarche, endometriosis-associated dyspareunia is suspected if pain develops after years of pain-free intercourse (Ferrero, 2005). The degree of discomfort, however, appears to be independent of disease severity (Fedele, 1992).

DYSURIA

Although less frequent symptoms of endometriosis, bladder complaints of painful urination as well as cyclic urinary frequency and urgency may be noted in affected women. Endometriosis may be suspected if these symptoms are concurrent with negative urine cultures (Vercellini, 1996a).

DEFECATORY PAIN

Painful defecation develops less commonly than the other manifestations of pelvic pain and typically reflects rectosigmoid involvement with endometriotic implants (Azzena, 1998). Symptoms may be chronic or cyclic, and they may be associated with constipation, diarrhea, or cyclic hematochezia (Remorgida, 2007).

NONCYCLICAL PELVIC PAIN

Chronic pelvic pain is the most common symptom associated with endometriosis. Approximately 40 to 60 percent of women with chronic pelvic pain are found to have endometriosis at the time of laparoscopy (Eskenazi, 1997). Some studies have demonstrated a correlation of pain severity with advanced stage disease, whereas other studies have not (Fedele, 1992; Muzii, 1997).

The focus of chronic pain may vary from woman to woman. If the rectovaginal septum or uterosacral ligaments are involved with disease, pain may radiate to the rectum or lower back. Alternatively, pain radiating down the leg and causing cyclic sciatica may reflect posterior peritoneal endometriosis or direct sciatic nerve involvement (Possover, 2007; Vercellini, 2003a; Vilos, 2002).

Infertility

The incidence of endometriosis in women with subfertility is 20 to 30 percent (Waller, 1993). In addition, although there is wide variability reported, patients with infertility appear to have a greater incidence of endometriosis than fertile controls (13 to 33 percent versus 4 to 8 percent) (D'Hooghe, 2003; Strathy, 1982). Furthermore, Matorras and colleagues (2001) noted an increased prevalence of more severe stages of endometriosis in women with infertility. This may result from adhesions which are caused by endometriosis and impair normal oocyte pick-up and transport by the fallopian tube. Beyond mechanical impairment of ovulation and fertilization, more subtle defects also appear to be involved in the pathogenesis of infertility in women with endometriosis. Such defects include perturbations in ovarian and immune function as well as implantation.

MINIMAL OR MILD DISEASE

Although evidence from animal studies suggest that severe forms of endometriosis are associated with infertility, support for an association and causation of infertility by milder forms of endometriosis is less abundant (D'Hooghe, 1996; Schenken, 1980). Primate studies have shown that surgically-induced endometriosis resulted in a 35-percent pregnancy rate in animals with minimal endometriosis, a 12 percent rate with advanced endometriosis, and no pregnancies if ovarian adhesions were present. These rates compared poorly with a 42-percent pregnancy rate in control animals (Schenken, 1984).

Human studies demonstrating a causation of subfertility by endometriosis are lacking, but an association is suggested by the

differing prevalence of endometriosis between infertile patients and fertile women.

Evaluating women with minimal disease, Rodriguez-Escudero and colleagues (1988) reported that women with minimal endometriosis had a monthly fecundity rate of 6 percent and a 12-month cumulative pregnancy rate of 47 percent. Although this is much lower than normal fertile women, participation bias likely exists in such studies. Furthermore, a prospective cohort study demonstrated that women with minimal or mild endometriosis had a similar fecundity compared with those with unexplained infertility. Well-designed, prospective randomized controlled trials (RCTs) have found conflicting evidence as to whether surgical treatment of endometriosis improves fecundity rates and cumulative pregnancy rates in these women. One of these studies demonstrated improved fertility, but a trial with fewer women noted no improvement (Marcoux, 1997; Parazzini, 1999).

MODERATE OR SEVERE DISEASE

In moderate to severe endometriosis (stage III to IV), tubal and ovarian architecture are often distorted. As a result, impaired fertility would be expected. Unfortunately, few studies report fecundity rates in women with severe endometriosis. One investigation comparing mild, moderate, and severe endometriosis revealed a monthly fecundity rate of 8.7 percent in those with mild disease, 3.2 percent with moderate disease, and no pregnancies with severe disease (Olive, 1985a). There are no well-designed studies examining the effectiveness of surgical therapy in patients with severe endometriosis, but cumulative pregnancy rates have reached 30 percent after surgical excision (Adamson, 1993; Osuga, 2002). This rate appears to be greater than that of women who undergo expectant management.

FOLLICULOGENESIS AND EMBRYOGENESIS EFFECTS

Some researchers have suggested that folliculogenesis is impaired in women with endometriosis. Embryo development and quality in women with endometriosis undergoing IVF was compared with that of embryos originating from women with tubal factor infertility (Pellicer, 1995). There were significantly fewer blastomeres per embryo and a significantly greater rate of embryonic developmental arrest in the endometriosis group. This suggests a possible decreased developmental competence of oocytes originating from the ovaries of women with endometriosis. Another investigation found that oocyte number may be decreased in women with endometriosis (Suzuki, 2005). In addition, researchers have attempted to determine if the follicular environment is different in women with endometriosis. Specifically, studies demonstrating qualitative and quantitative changes in steroidogenesis, however, have found conflicting results (Garrido, 2002; Harlow, 1996; Pellicer, 1998). Apoptosis is another attractive theory for decreased oocyte competence in women with endometriosis, but well-designed studies are lacking.

ENDOMETRICAL CHANGES

Abnormalities in endometrial development in women with endometriosis support the possibility that implantation defects may be responsible for subfertility associated with endometriosis. For example, researchers have revealed abnormalities in gene expression profiles in the eutopic endometrium from women with endometriosis compared with that from women without endometriosis (Kao, 2003). Specifically, deficient $\alpha_v \beta_3$ integrin expression in the peri-implantation endometrium of women with endometriosis has been demonstrated, and this may be associated with decreased uterine receptivity (Lessey, 1994). The role of apoptosis on peri-implantation endometrium is another area of study that still remains largely unexplored.

OTHER FACTORS

Abnormalities in inflammation and cytokine activity in women with endometriosis may play a role in endometriosis-associated infertility. Sperm function may be affected in women with endometriosis. Studies have demonstrated increased phagocytosis of spermatozoa by macrophages from women with endometriosis (Haney, 1981; Muscato, 1982). Moreover, sperm binding to the zona pellucida appears to be adversely affected (Qiao, 1998). However, investigations of the effects of endometriosis on sperm motility and the acrosome reaction reveal conflicting results (Bielfeld, 1993; Curtis, 1993; Tasdemir, 1995).

Intestinal Obstruction

Endometriosis may involve the small bowel, cecum, appendix, or rectosigmoid colon and lead to intestinal obstruction in some cases (Cameron, 1995; Varras, 2002; Wickramasekera, 1999). Although endometriosis of the gastrointestinal tract is usually confined to the subserosa and muscularis propria, more severe cases may involve the bowel wall transmurally and lead to a clinical and radiologic picture consistent with malignancy (Decker, 2004). Accurate preoperative diagnosis and management are difficult

due to the atypical presentation. Laparoscopy typically provides the definitive diagnosis. Treatment is often surgical, with resection and primary anastomosis of the affected intestinal segment. In women without obstructing symptoms, however, conservative management with hormonal therapy may be considered.

DIFFERENTIAL DIAGNOSIS

The symptoms of endometriosis are nonspecific and may mimic many disease processes. Because endometriosis is a surgical diagnosis, several other diagnoses may be considered prior to surgical exploration (Table 10-1).

Table 10-1 Differential Diagnosis of Endometriosis
Gynecologic
Pelvic inflammatory disease
Tubo-ovarian abscess
Salpingitis
Endometritis
Hemorrhagic ovarian cyst
Ovarian torsion
Primary dysmenorrhea
Degenerating leiomyoma
Nongynecologic
Interstitial cystitis
Chronic urinary tract infection
Renal calculi
Inflammatory bowel disease
Irritable bowel syndrome
Diverticulitis
Mesenteric lymphadenitis
Musculoskeletal disorders

DIAGNOSIS

Physical Examination

VISUAL INSPECTION

For the most part, endometriosis is a disease confined to the pelvis. Accordingly, there are often no abnormalities on visual inspection. Some exceptions include endometriosis within an episiotomy scar or surgical scar, most often within a Pfannenstiel incision (Fig. 10-4) (Koger, 1993; Zhu, 2002). Rarely, endometriosis may develop spontaneously within the perineum or perianal

region (Watanabe, 2003).

FIGURE 10-4

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Endometriosis within a lower vertical midline incision scar (arrows).

SPECULUM EXAMINATION

Examination of the vagina and cervix by speculum examination often reveals no signs of endometriosis. Occasionally, bluish or red powder-burn lesions may be seen on the cervix or the posterior fornix of the vagina. These lesions may be tender or bleed with contact. One recent study found that speculum examination displayed endometriosis in 14 percent of patients diagnosed with deeply infiltrating endometriosis (Chapron, 2002).

BIMANUAL EXAMINATION

Pelvic organ palpation often reveals anatomic abnormalities suggestive of endometriosis. Uterosacral ligament nodularity and tenderness may reflect active disease or scarring along the ligament. In addition, an enlarged cystic adnexal mass may represent an ovarian endometrioma, which may be mobile or adherent to other pelvic structures. Bimanual examination may reveal a retroverted, fixed, tender uterus, or a firm, fixed posterior cul-de-sac.

Although pelvic organ palpation may assist in the diagnosis, the sensitivity and specificity of focal pelvic tenderness in detecting endometriosis displays wide variation and ranges from 36 to 90 percent and 32 to 92 percent, respectively (Chapron, 2002;

Eskenazi, 2001; Koninckx, 1996; Ripps, 1992). For example, Chapron and co-workers (2002) palpated a painful nodule in 43 percent of patients with deeply infiltrating endometriosis. In another study of 91 women with chronic pelvic pain and surgically confirmed endometriosis, the bimanual examination was normal 47 percent of the time (Nezhat, 1994). One study suggested that pelvic nodularities secondary to endometriosis may be more easily detected by bimanual examination during menses (Koninckx, 1996).

Laboratory Testing

To exclude other causes of pelvic pain, laboratory investigations are often undertaken. Initially, a complete blood count (CBC), urinalysis and urine cultures, vaginal cultures, and cervical swabs may be obtained to exclude infections or sexually transmitted infections that may cause pelvic inflammatory disease (see Chap. 3, Pelvic Inflammatory Disease).

SERUM CA125

Numerous serum markers have been studied as possible adjuncts in the diagnosis of endometriosis. No serum marker has been studied in greater detail than CA125 (cancer antigen 125). Found as an antigenic determinant on a glycoprotein, CA125 has been identified in several adult tissues such as the epithelium of the fallopian tubes, the endometrium, the endocervix, the pleura, and the peritoneum (see Chap. 35, Laboratory Testing). Recognized by monoclonal antibody assays, elevated CA125 levels have been shown to positively correlate with the severity of endometriosis (Hornstein, 1995a). Unfortunately, although demonstrating adequate specificity, the assay has poor sensitivity in detecting mild endometriosis. A meta-analysis of studies evaluating CA125 in the diagnosis of endometriosis revealed a sensitivity of only 28 percent and a specificity of 90 percent (Mol, 1998). This marker appeared to be a better test in diagnosing stage III and IV endometriosis. Although the role of this test in clinical practice is uncertain, it may be useful in the presence of a sonographically detected ovarian cyst suggestive of an endometrioma.

OTHER SERUM MARKERS

Cancer antigen 19-9 (CA 19-9), another antigenic glycoprotein, is a serum marker that has also been shown to positively correlate with the severity of endometriosis (Harada, 2002). Serum placental protein 14 (PP14; glycodelin-A) was initially shown to have adequate sensitivity (59 percent), but this has not been confirmed by other studies (Telimaa, 1989). Interleukin-6 (IL-6) serum levels above 2 pg/mL (90-percent sensitivity and 67-percent specificity) and tumor necrosis factor-α (TNF-α) peritoneal fluid levels above 15 pg/mL (100-percent sensitivity and 89-percent specificity) may be used to discriminate between those with or without endometriosis (Bedaiwy, 2002). Several other serum markers have been studied, with limited diagnostic accuracy (Bedaiwy, 2004). Most of these tests are rarely used outside of research settings.

Diagnostic Imaging

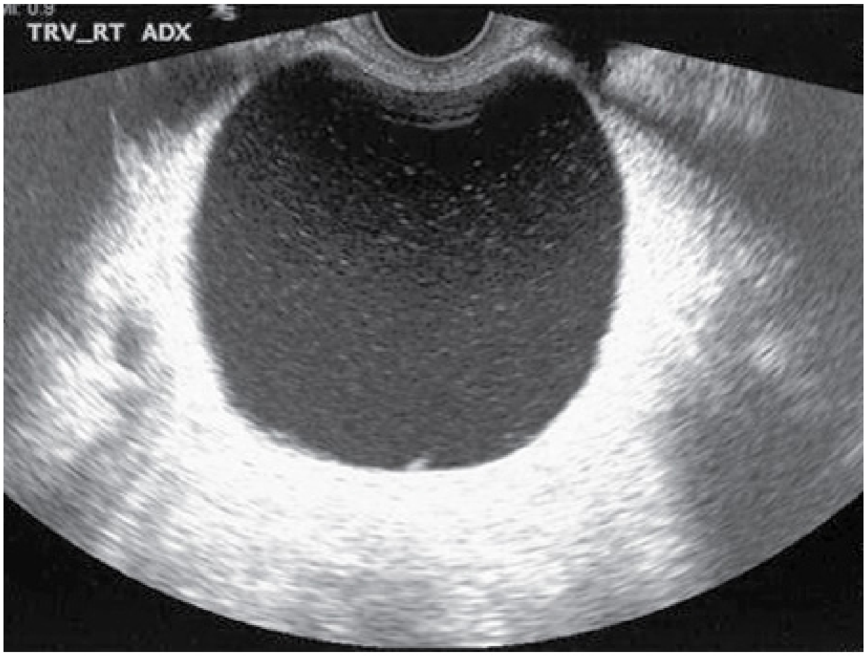
SONOGRAPHY

Both transabdominal and the more sensitive transvaginal (TVS) sonographic approaches have been used extensively in the diagnosis of endometriosis (see Chap. 2). Although TVS is the mainstay in evaluating symptoms associated with endometriosis and is accurate in detecting endometriomas, imaging of superficial endometriosis or endometriotic adhesions is inadequate. Small endometriotic plaques or nodules may occasionally be seen, but these findings are inconsistent (Carbognin, 2004).

More recently, sonovaginography, a technique involving vaginal saline instillation to more accurately localize rectovaginal endometriosis, and transrectal sonography have assisted in the diagnosis and evaluation of endometriosis (Brosens, 2003). Transvaginal sonography appears to be as effective as a transrectal approach in identifying posterior pelvic endometriosis, but the latter may delineate rectal involvement more accurately and may be more appropriate when planning surgery (Bazot, 2003).

Endometriomas can be diagnosed by TVS with adequate sensitivity in most settings if they are 20 mm in diameter or greater (Fig. 10-5). Specifically, sensitivity and specificity of TVS to diagnose endometriomas range from 64 to 90 percent and from 22 to 100 percent, respectively (Moore, 2002). Endometriomas often present as cystic structures with low-level internal echoes, and occasional thick septations, thickened walls, and echogenic wall foci (Athey, 1989; Patel, 1999). Color Doppler transvaginal sonography often demonstrates pericystic, but not intracystic, flow (Carbognin, 2004).

FIGURE 10-5



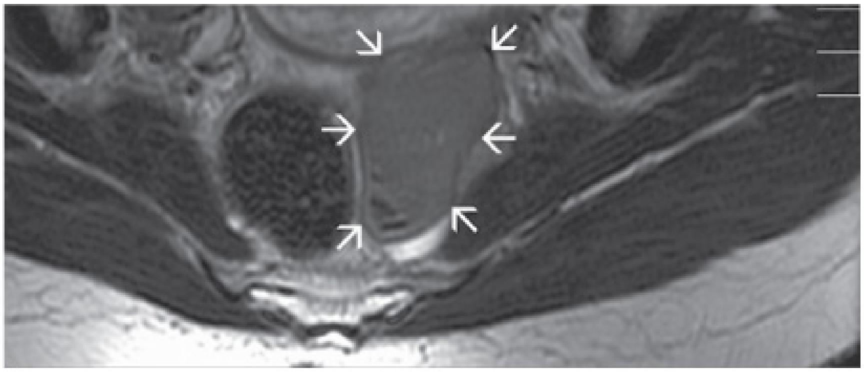
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Transvaginal sonogram demonstrating ovarian endometrioma. A cyst with diffuse internal low-level echoes is seen. *(Courtesy of Dr. Elysia Moschos.)*

MAGNETIC RESONANCE IMAGING

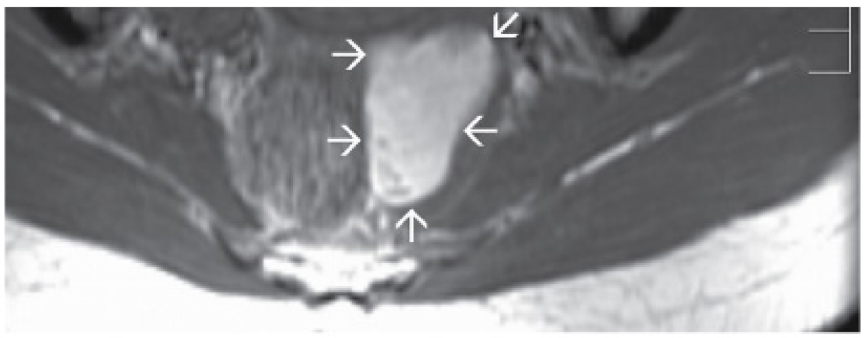
Magnetic resonance imaging has been increasingly used as a noninvasive method for diagnosis of endometriosis. Small nodules may be recognized as hyperintense lesions on T1-weighted sequences, and plaque lesions have a similar appearance, with a variable signal on T2-weighted sequences (Carbognin, 2004). An endometrioma appears as a hyperintense mass on T1-weighted sequences, with a tendency towards hypointensity in T2-weighted sequences. A hypointense ring is often seen surrounding the endometrioma, which is enhanced after contrast administration (Fig. 10-6).

FIGURE 10-6



A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Magnetic resonance images of an endometrioma. T2- (**A**) and T1-weighted (**B**) images reveal an endometrioma (**arrows**) just lateral to the rectum. The findings are consistent with subacute blood, based on the bright signal on T-1 and the relatively low signal intensity on T-2 of the lesion. *(Courtesy of Dr. Diane Twickler.)*

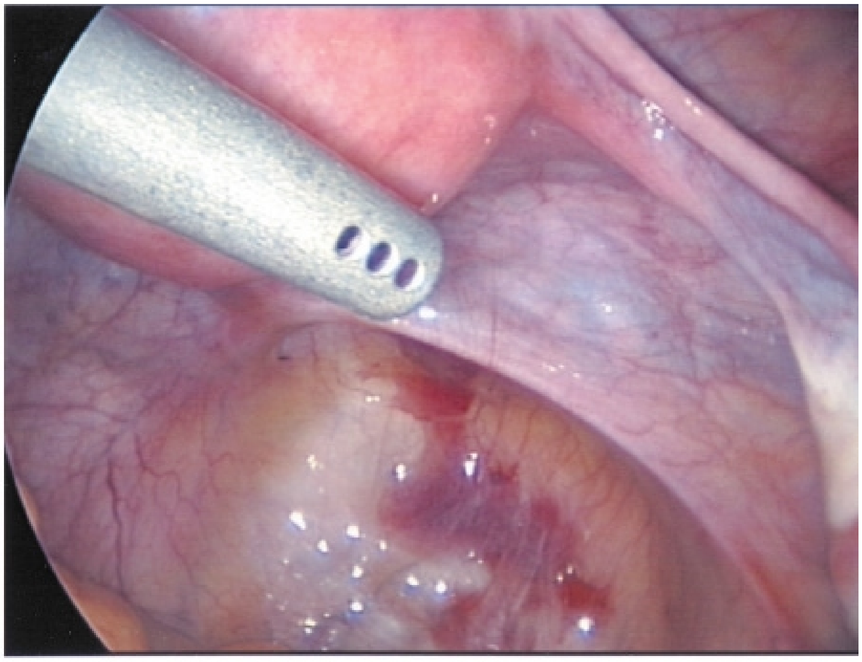
Diagnostic Laparoscopy

Diagnostic laparoscopy is the primary method used for diagnosing endometriosis (see Section 41-28, Laparoscopy) (Kennedy, 2005). Laparoscopic findings are variable and may include discrete endometriotic lesions, endometrioma, and adhesion formation.

ENDOMETRIOTIC LESIONS

The pelvic organs and pelvic peritoneum are typical locations for endometriosis. The appearance of these lesions by laparoscopy is varied and colors may include red (red, red-pink, or clear), white (white or yellow-brown), and black (black or black-blue) (Fig. 10-7). Dark lesions are pigmented by hemosiderin deposition from trapped menstrual debris. White and red lesions most commonly correlate with the histologic findings of endometriosis (Jansen, 1986). In addition to color differences, endometriotic lesions may differ morphologically. They can appear as smooth blebs on peritoneal surfaces, as holes or defects within the peritoneum, or as flat stellate lesions whose points are formed by surrounding scar tissue. Endometriotic lesions may be superficial or may deeply invade the peritoneum or pelvic organs. Although these findings may allow endometriosis to be diagnosed with accuracy, pain symptoms correlate poorly with findings at laparoscopy (Kennedy, 2005).

FIGURE 10-7



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Below the irrigator tip, a red and white endometriotic lesion is seen on the pelvic peritoneum during laparoscopy. *(Courtesy of Dr. Karen Bradshaw.)*

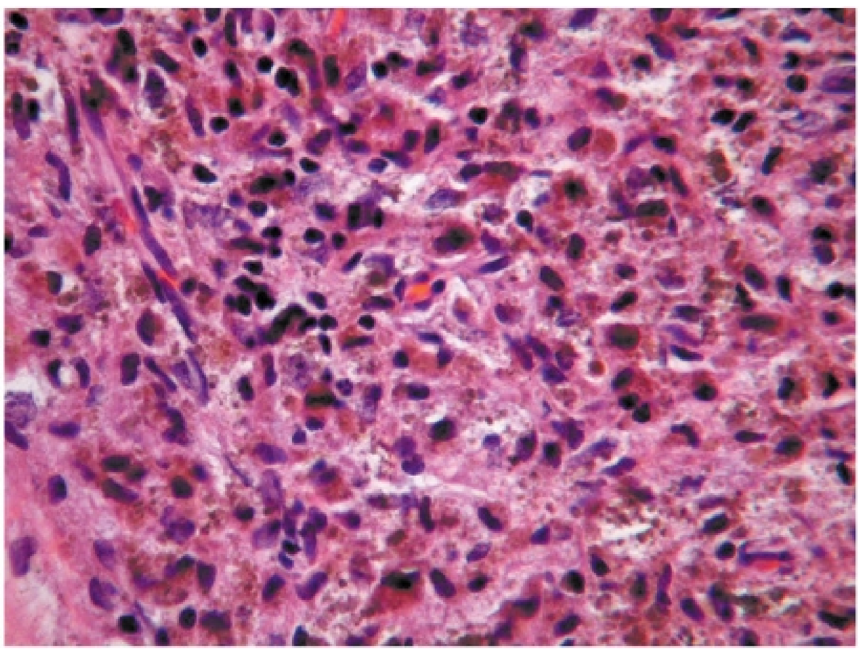
ENDOMETRIOMAS

Endometriomas are cystic endometrial lesions contained within the ovary. Typically, they have the appearance of smooth-walled, brown cysts filled with thick, chocolate-appearing liquid (Fig. 10-8). These ovarian masses may be unilocular, but are often multilocular when >3 cm in diameter (Nezhat, 1992b).

FIGURE 10-8

A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

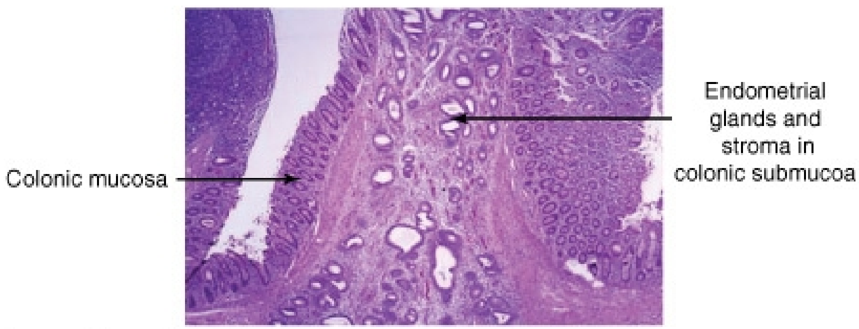
Photographs of an endometrioma. **A.** A bisected endometrioma showing a shaggy hemorrhagic lining. **B.** Microscopic image of an endometrioma showing predominantly hemosiderin-laden macrophages resulting in the brown discoloration. *(Courtesy of Dr. Raheela Ashfaq.)*

Laparoscopic visualization of ovarian endometriomas has a sensitivity and specificity of 97 percent and 95 percent, respectively (Vercellini, 1991). Because of this, ovarian biopsy is rarely required for diagnosis.

Pathologic Analysis

Although current guidelines do not require histologic evaluation for the diagnosis of endometriosis, some suggest that relying solely on laparoscopic findings in the absence of histologic confirmation often results in overdiagnosis (American Society for Reproductive Medicine, 1997). Specifically, the greatest discordance between laparoscopic and histologic findings is noted in scarred lesions (Marchino, 2005a; Walter, 2001). Histologic diagnosis requires the presence of both endometrial glands and stroma found outside the uterine cavity (Fig. 10-9). Additionally, hemosiderin deposition and fibromuscular metaplasia are frequently noted (Murphy, 2002). The gross appearance of endometriotic lesions often suggests certain microscopic findings. For example, when examined microscopically, red lesions are frequently vascularized, whereas white lesions more often display fibrosis and few vessels (Nisolle, 1997).

FIGURE 10-9



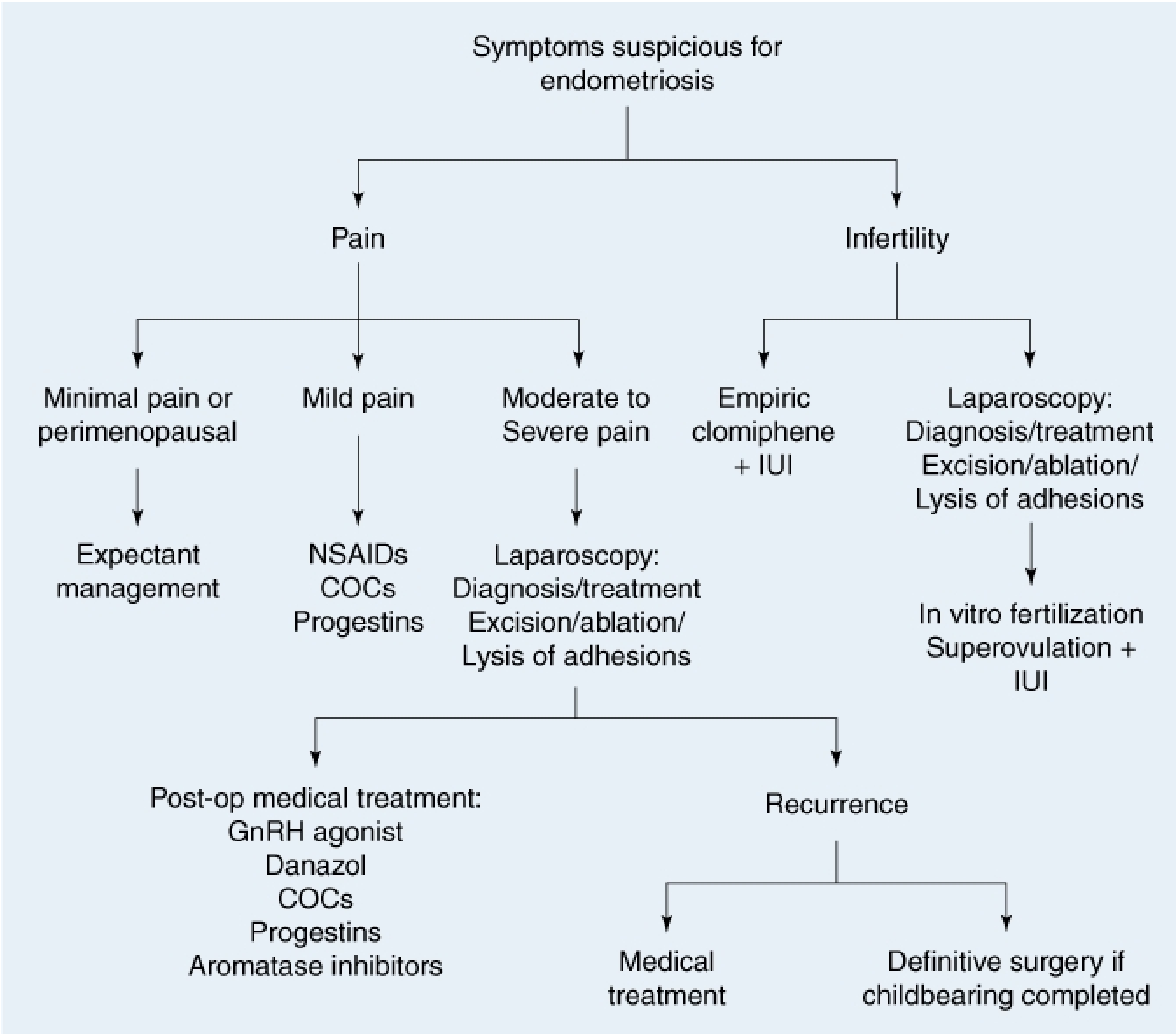
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Colonic endometriosis. Note the benign endometrial glands and endometrial stroma in the colonic submucosa. *(Courtesy of Dr. Raheela Ashfaq.)*

Diagnostic Algorithm

The approach to diagnosis and treatment of endometriosis depends on the presenting symptoms and goals of therapy (Fig. 10-10). If infertility is the presenting symptom, then fertility-preserving treatment without ovulation suppression will be required. In contrast, if the patient has severe, recalcitrant pain symptoms and has completed childbearing, definitive surgery may be warranted.

FIGURE 10-10



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Diagnostic and treatment algorithm for women with presumptive or proven endometriosis. COCs = combination oral contraceptives; GnRH = gonadotropin-releasing hormone; IUI = intrauterine insemination; NSAIDs = nonsteroidal anti-inflammatory drugs.

TREATMENT

Treatment for endometriosis depends on the woman's specific symptoms, severity of symptoms, location of endometriotic lesions, goals for treatment, and desire to conserve future fertility. The most important factor when determining the most appropriate management is whether a patient is seeking treatment for infertility or pain, as the treatment will differ based on the symptom (Olive, 2001).

Expectant Management

For many women, symptoms will preclude them from choosing expectant management. However, for those with mild symptoms or

for asymptomatic women diagnosed incidentally, expectant management may be appropriate. For example, Sutton and associates (1997) expectantly managed patients initially diagnosed by laparoscopy with minimal to moderate endometriosis. At second-look laparoscopy after 1 year, 29 percent of women had disease regression, 42 percent remained unchanged, and 29 percent had disease progression. Other investigations have shown similar rates of disease regression with expectant management (Thomas, 1987). However, studies evaluating infertile women have demonstrated lower fecundity rates after expectant management than following surgical treatment (Milingos, 2002; Marcoux, 1997). These studies are confined to patients with minimal to moderate endometriosis, and there are no well-designed trials examining the effect of expectant management on severe endometriosis.

Medical Treatment of Endometriosis-Related Pain

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

These agents nonselectively inhibit the cyclooxygenase isoenzymes 1 and 2 (COX-1 and COX-2), and within this group, the selective COX-2 inhibitors selectively inhibit the COX-2 isoenzyme. These enzymes are responsible for the synthesis of prostaglandins involved in the pain and inflammation associated with endometriosis. For example, endometriotic tissue has been shown to express COX-2 at greater levels than eutopic endometrium (Ota, 2001). Therefore, therapy aimed at lowering these prostaglandin levels may play a role in alleviating endometriosis-associated pain.

Nonsteroidal anti-inflammatory drugs are often first-line therapy in women with primary dysmenorrhea or pelvic pain prior to laparoscopic confirmation of endometriosis, and in women with minimal or mild pain symptoms associated with known endometriosis. Although animal models have demonstrated disease regression with NSAID treatment, few studies have critically evaluated their effectiveness in disease regression in surgically-confirmed endometriosis (Efstathiou, 2005). However, evidence exists for their efficacy in patients with dysmenorrhea and pelvic pain (Table 10-2) (Nasir, 2004). Due to the cardiovascular risks with long-term use of COX-2 inhibitors, these medications should be used at the lowest possible dose and for the shortest duration necessary (Jones, 2005).

Table 10-2 Commonly Used Oral Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) in the Treatment of Endometriosis-Associated Dysmenorrhea

Generic Name	Trade Name	Dosage	Adverse Effects
Ibuprofen	Motrin, Advil, Nuprin	400 mg every 4â€“6 h	Nausea; epigastric pain; anorexia; constipation; gastrointestinal bleeding
Naproxen	Naprosyn, Aleve	500 mg initially, then 250 mg every 6â€“8 h	Same as above
Naproxen sodium	Anaprox	550 mg initially, then 275 mg every 6â€“8 h	Same as above
Mefenamic acid	Ponstel	500 mg initially, then 250 mg every 6 h, starting with menses and continued for 3 days	Same as above
Ketoprofen	Orudis, Oruvail	50 mg q6â€“8 h	Same as above

COMBINATION ORAL CONTRACEPTIVES

These agents have been a mainstay for the treatment of pain associated with endometriosis. Although no randomized controlled trials have compared COCs with placebo, abundant observational evidence supports the role of COCs in the relief of endometriosis-related pain (Vercellini, 1993; Vessey, 1993). These drugs appear to act by inhibiting gonadotropin release, decreasing menstrual flow, and decidualizing implants. In addition, COCs have the added benefit of contraception, suppression of ovulation, and other noncontraceptive benefits (see Table 5-6).

These drugs can be used conventionally in a cyclic regimen or may be used continuously, without a break for withdrawal menses. The continuous regimen may be preferable for its decreased frequency of menses for women who fail to achieve pain relief with cyclic COC therapy (Vercellini, 2003b; Wiegratz, 2004). Traditionally, monophasic COCs have been used in the treatment of endometriosis, but no evidence supports their clinical superiority to multiphasic COCs. Additionally, low-dose COCs (containing 20 μg ethinyl estradiol) have not proved superior to conventional-dose COCs for the treatment of endometriosis and may lead to higher rates of abnormal bleeding (Gallo, 2005).

PROGESTINS

Progestational agents have long been used in the treatment of endometriosis. Progestins are known to antagonize estrogenic effects on the endometrium, causing initial decidualization and subsequent endometrial atrophy. Progestins have been administered for the treatment of endometriosis in numerous ways and include oral progestins, depot medroxyprogesterone acetate (DMPA), a levonorgestrel-releasing intrauterine device (IUD), and the newer selective progesterone-receptor modulators (SPRMs).

Although progestin-based therapy is commonly used to effectively treat symptoms, there has been only one well-designed, randomized controlled trial comparing the effect of placebo with medroxyprogesterone acetate (MPA), 100 mg orally daily, given for 6 months. At second-look laparoscopy, partial or total resolution of peritoneal implants in 60 percent of women was noted, compared with 18 percent in the placebo group. Furthermore, pelvic pain and defecatory pain were significantly reduced (Telimaa, 1987). Side effects of high-dose MPA included acne, edema, weight gain, and irregular menstrual bleeding. In practice, MPA is prescribed in dosages ranging from 20 to 100 mg daily. Alternatively, MPA may be given intramuscularly in depot form in a dosage of 150 mg every 3 months. In depot form, MPA may delay resumption of normal menses and ovulation and should not be used in women contemplating imminent pregnancy.

Norethindrone acetate (NETA) is a 19-nortestosterone synthetic progestin that has been used in the treatment of endometriosis. In one study, investigators administered an initial oral dosage of NETA, 5 mg daily, with increases of 2.5 mg daily until amenorrhea or a maximal dosage of 20 mg daily was reached. They found an approximately 90-percent reduction in dysmenorrhea and pelvic pain (Muneyyirci-Delale, 1998). Additionally, NETA has been shown to be effective in conjunction with long-term gonadotropin-releasing hormone (GnRH) agonist therapy for endometriosis. In this fashion, NETA, 5 mg administered orally daily, in conjunction with prolonged GnRH agonist therapy, results in significant resolution of symptoms while protecting against bone loss (Hornstein, 1998; Surrey, 2002).

The levonorgestrel-releasing intrauterine system (LNG-IUS) (Mirena, Berlex, Montville, NJ) has traditionally been used for contraception and dysfunctional uterine bleeding (see Fig. 5-5). Recently, the LNG-IUS, however, has been used for the treatment of endometriosis. This IUD delivers levonorgestrel directly to the endometrium and is effective for up to 5 years. An observational trial revealed symptomatic improvement in patients with endometriosis using the LNG-IUS, with symptom improvement continuing up to 30 months (Lockhat, 2005). The continuation rate at 3 years, however, was only 56 percent, mostly due to intolerable bleeding, persistent pain, and weight gain. A randomized controlled trial comparing LNG-IUS with GnRH agonist therapy showed equivalent improvement in pain symptoms, without the concomitant hypoestrogenism that accompanies GnRH agonist treatment (Petta, 2005). Accordingly, these recent findings make the LNG-IUS an attractive option in treating women with endometriosis.

SELECTIVE PROGESTERONE RECEPTOR MODULATORS

A new and novel option in the treatment of endometriosis has been the use of selective progesterone-receptor modulators (SPRMs). These are progesterone-receptor ligands (molecules that bind and activate or inactivate the progesterone receptor) and have both progesterone antagonist and antagonist activities (Elger, 2000). One common SPRM, mifepristone (RU486), is a controversial abortifacient that predominantly possesses antiprogestational activity. It has also been studied in women with endometriosis and was found to reduce pelvic pain and extent of endometriosis, when used for 6 months at oral dosages of 50 mg daily (Kettel, 1996). Asoprisnil (J867) is a SPRM that induces endometrial atrophy and amenorrhea. Currently in Phase III trials for the treatment of leiomyomas and endometriosis, asoprisnil in Phase II studies improved dysmenorrhea and pelvic pain symptoms, whereas amenorrhea was dose dependent (Chwalisz, 2005). These novel agents hold promise for future treatment of endometriosis.

ANDROGENS

The first medication approved for the treatment of endometriosis in the United States was the androgen danazol. This agent is a synthetic androgen that is an isoxazole derivative of 17-α-ethinyl testosterone. The predominant mechanism of action appears to be suppression of midcycle luteinizing hormone (LH) surge, creating a chronic anovulatory state (Floyd, 1980). Danazol occupies receptor sites on sex-hormone binding globulin (SHBG) to increase serum free testosterone levels and also binds directly to androgen and progesterone receptors. As a result, danazol creates a hypoestrogenic, hyperandrogenic state, inducing endometrial atrophy in endometriotic implants (Fedele, 1990).

Danazol at dosages of 200 mg given orally three times daily proved superior to placebo for the reduction of endometriotic implants and pelvic pain symptoms after 6 months of therapy (Telimaa, 1987). The recommended dosage of danazol is 600 to 800 mg daily. Unfortunately, significant androgenic side effects develop at this dosage and include acne, hot flashes, hirsutism, adverse serum lipid profiles, voice deepening (possibly irreversible), elevation of liver enzymes, and mood changes. Moreover, due to possible teratogenicity, this medication should be taken in conjunction with effective contraception. Because of this adverse side-effect profile, danazol is prescribed less frequently, and when administered, its duration should be limited.

Gestrinone (ethylnorgestrienone; R2323) is an antiprogestational agent prescribed in Europe for the treatment of endometriosis. Although it has antiprogestational, antiestrogenic, and androgenic effects, it predominantly induces a progesterone withdrawal effect and decreases the number of estrogen and progesterone receptors. Endocrinologic changes during therapy with gestrinone show that basal concentrations of gonadotropin levels remain unchanged, estradiol concentrations vary, and free testosterone levels increase, with concomitant androgenic side effects (Forbes, 1993).

Gestrinone equals the effectiveness of danazol and of GnRH agonists for relief of endometriosis-related pain (Prentice, 2000a). Furthermore, during 6 months of treatment, gestrinone was not associated with the bone density loss commonly seen with GnRH agonist use and was more effective in persistently decreasing moderate to severe pelvic pain (Gestrinone Italian Study Group, 1996). Unfortunately, gestrinone appears to lower high-density lipoprotein (HDL) levels. Gestrinone is administered orally, 2.5 to 10 mg weekly, given daily or three times weekly.

GNRH AGONISTS

Endogenous pulsatile release of GnRH leads to pulsatile secretory activity of the gonadotropes within the anterior pituitary. This pulsatile release results in pituitary release of gonadotropins, with subsequent ovarian steroidogenesis and ovulation. Continuous, nonpulsatile GnRH administration, however, results in pituitary desensitization and subsequent loss of ovarian steroidogenesis (Rabin, 1980). These features allow pharmacologic use of GnRH agonists for the treatment of endometriosis. With loss of ovarian estradiol production, the hypoestrogenic environment removes the stimulation normally provided to the endometriotic implants and creates a pseudomenopausal state during treatment.

Pain Improvement

Agonists may be used prior to laparoscopy in women with chronic pelvic pain and clinical suspicion of endometriosis. A list of clinically used GnRH agonists is found in Table 9-3. After 3 months of GnRH agonist treatment (depot leuprolide acetate; Lupron Depot, TAP Pharmaceutical Products, Lake Forest, IL), pain scores were significantly reduced compared with placebo (Ling, 1999). Subsequent laparoscopy revealed that 93 percent of these women had surgically-diagnosed endometriosis. Accordingly, many suggest that in similar patients, depot leuprolide acetate may be used empirically in lieu of laparoscopy, for satisfactory improvement in symptoms.

Numerous studies have demonstrated the effectiveness of GnRH agonist therapy to improve pain symptoms in women with surgically-confirmed endometriosis. For example, in their randomized controlled trial, Dlugi and co-workers (1990) compared depot leuprolide acetate with placebo and found significant decreases in the severity of pelvic pain. Similar findings were obtained comparing buserelin, another GnRH agonist, with expectant management during a 6-month period (Fedele, 1993). The GnRH agonists seem to provide greater relief when administered for 6 months compared with 3 months (Hornstein, 1995b).

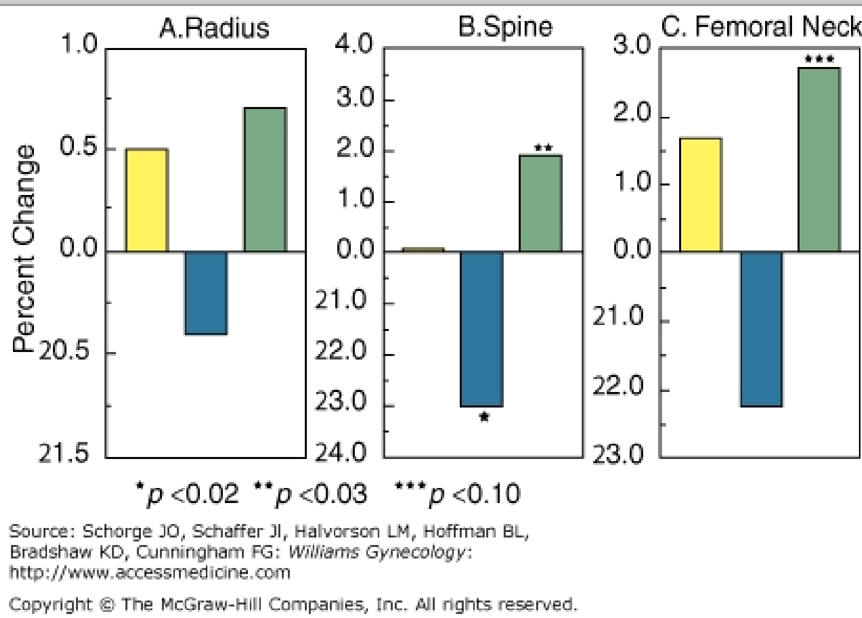
In trials with other drugs for the treatment of endometriosis, GnRH agonists compared favorably. Vercellini and associates (1993), in their randomized controlled trial found equal degrees of pain improvement when comparing GnRH agonist therapy with a low-dose cyclic COC regimen. Dyspareunia, however, was less in the GnRH agonistâ€“treated group. In addition, a meta-analysis

revealed that GnRH agonists were equally effective in improving pain scores and decreasing endometriotic implants compared with danazol (Prentice, 2000b).

Add-Back Therapy

Concerns about the long-term effects of prolonged hypoestrogenism preclude extended treatment with GnRH agonists. Hypoestrogenic symptoms include hot flushes, insomnia, reduced libido, vaginal dryness, and headaches. Of particular concern is the effect of the hypoestrogenic state on bone mineral density (BMD). Evidence indicates that there are decreases in spine and hip BMD at 3 and 6 months of GnRH agonist therapy, with only partial recovery at 12 to 15 months after treatment (Orwoll, 1994). Because of the increased risk of osteoporosis, therapy is usually limited to the shortest possible duration (usually no greater than 6 months). Additionally, estrogen in the form of COCs may be added to GnRH agonist therapy to counteract the bone loss and is termed *add-back therapy* (Fig. 10-11) (Carr, 1995). Occasionally a GnRH agonist may be used for longer periods, with hormonal add-back therapy in the form of norethindrone acetate, 5 mg orally given daily, with or without conjugated equine estrogen (Premarin, Wyeth, Madison, NJ) 0.625 mg daily for 12 months. This regimen has been shown to provide extended pain relief beyond the duration of treatment and preservation of bone density (Surrey, 2002).

FIGURE 10-11



Changes in bone mineral density in the radius, spine, and femoral neck in women treated for 6 months with oral contraceptive pills (**yellow**), gonadotropin-releasing hormone agonist (**blue**), or gonadotropin-releasing hormone agonist plus oral contraceptive pills (**green**)*. (From Carr, 1995, with permission).*

AROMATASE INHIBITORS

As previously mentioned, endometrial tissue locally produces aromatase, the enzyme responsible for estrogen synthesis. In endometriotic tissue, estrogen may be produced locally through aromatization of circulating androgens. This may be the reason for postmenopausal endometriosis and for intractable symptoms in some women despite treatment. An aromatase inhibitor was first used for endometriosis treatment in a woman with postmenopausal endometriosis after total hysterectomy and bilateral salpingo-oophorectomy (Takayama, 1998). The patient experienced significant pain relief, significant endometriotic lesion size reduction, and a 6-percent reduction in lumbar spine BMD after 9 months of treatment. Subsequently, further study has examined aromatase inhibitors in conjunction with low-dose, continuous COC add-back therapy for 6 months. This small Phase II trial revealed a significant pain reduction in 14 of 15 women with previously intractable pain from endometriosis (Amsterdam, 2005). Aromatase inhibitors have similar hypoestrogenic side-effect profiles as GnRH agonists, but hold promise in severe, refractory cases of endometriosis.

Surgical Treatment of Endometriosis-Related Pain

LESION REMOVAL AND ADHESIOLYSIS

Because the primary method for diagnosis of endometriosis is laparoscopy, surgical treatment of endometriosis at the time of diagnosis is an attractive option. There are numerous studies examining removal of endometriotic lesions, either through excision or ablation. Unfortunately, many of these studies are uncontrolled or retrospective. However, a single randomized controlled trial comparing laparoscopic ablation of endometriotic lesions and laparoscopic uterine nerve ablation with diagnostic laparoscopy performed alone revealed significant symptom relief in 63 percent of women in the ablation group, compared with 23 percent in the expectant management group. Unfortunately, recurrence is common following surgical excision. Jones (2001) demonstrated pain recurrence in 74 percent of patients at a mean time following surgery of 73 months. The median time for recurrence was 20 months.

The optimal method of endometriotic implant ablation for maximal symptom relief is controversial. Laser ablation does not appear to be more effective than conventional electrosurgical ablation of endometriosis (Blackwell, 1991). A randomized controlled trial comparing ablation with excision of endometriotic lesions in women with stage I or II endometriosis revealed similar reductions in pain scores at 6 months (Wright, 2005). For deeply infiltrative endometriosis, some authors have advocated radical surgical excision, although well-designed trials are lacking (Chapron, 2004).

Adhesiolysis is postulated to effectively treat pain symptoms in women with endometriosis by restoring normal anatomy. Unfortunately, most studies are poorly designed and retrospective. As a result, a definitive link between adhesions and pelvic pain is unclear (Hammoud, 2004). For example, one randomized controlled trial demonstrated no overall pain relief from adhesiolysis compared with expectant management (Peters, 1992). However, within this study, one woman with severe, dense vascularized bowel adhesions experienced pain relief following adhesiolysis.

ENDOMETRIOMA RESECTION

Endometriomas are often treated surgically, as ovarian masses often prompt surgical investigation, and their associated symptoms may lead to more aggressive therapy (see Chap. 9, Surgical Excision). Historically, endometriomas have been treated by total ovarian cystectomy or by aspiration coupled with ablation of the cyst capsule (see Section 41-33, Laparoscopic Ovarian Cystectomy). One randomized controlled trial has compared cystectomy with surgical drainage and bipolar coagulation of the endometrioma's inner lining (Beretta, 1998). Cystectomy lead to lower rates of pelvic pain compared with drainage and coagulation (10 percent versus 53 percent). Additionally, cumulative pregnancy rates were higher following cystectomy during 24-month surveillance (67 percent versus 24 percent). Endometriomas may recur. Liu and co-workers (2007) found an approximately 15-percent rate of recurrence at 2 years following initial surgery.

PRESACRAL NEURECTOMY

For some women, transection of presacral nerves lying within the interiliac triangle may provide relief of chronic pelvic pain. Results from a recent randomized controlled trial revealed significantly greater pain relief at 12 months postoperatively in women treated with presacral neurectomy (PSN) and endometriotic excision compared with endometriotic excision alone (86 percent versus 57 percent) (Zullo, 2003). However, all of these women had midline pain, and an earlier meta-analysis demonstrated a significant decrease in pelvic pain after PSN compared with that following more conservative procedures, but only in those with midline pain (Wilson, 2000). Neurectomy may be performed laparoscopically, but it is technically challenging. For these reasons, PSN is used in a limited manner and not recommended routinely for management of endometriosis-related pain.

ABDOMINAL VERSUS LAPAROSCOPIC APPROACH

All of the surgical procedures listed above can be approached either through laparotomy or laparoscopy. Operative laparoscopy has been used for treatment of ovarian endometriomas for over 20 years, and strong evidence supports laparoscopy over laparotomy in managing benign ovarian masses (see Chap 9, Laparoscopy) (Mais, 1995; Reich, 1986; Yuen, 1997). Unfortunately, a large number of endometriomas are still treated by laparotomy, with 50 percent of physicians surveyed in the United Kingdom still treating endometriomas in this manner (Jones, 2002). Although laparoscopic treatment of endometrioma carries an associated 5 percent risk for conversion to laparotomy, because of its efficacy and low rates of postoperative morbidity, laparoscopy should be

the primary procedure of choice (Canis, 2003).

Studies also demonstrate the effectiveness and low morbidity rates in laparoscopic excision of endometriotic implants, and laparoscopic presacral neurectomy appears to be as effective as laparotomy (Nezhat, 1992a; Redwine, 1991). Moreover, adhesiolysis should be performed by laparoscopy when safe, and laparoscopy leads to less de novo adhesion formation than laparotomy (Gutt, 2004).

HYSTERECTOMY WITH BILATERAL OOPHORECTOMY

Hysterectomy with bilateral oophorectomy is the definitive and most effective therapy for women with endometriosis who do not wish to retain their reproductive function. Women who forego bilateral oophorectomy during hysterectomy for endometriosis have a sixfold greater risk of recurrent chronic pelvic pain (CPP) and an eightfold greater risk of requiring additional surgery compared with women who undergo concomitant bilateral oophorectomy (Namnoum, 1995). For this reason, hysterectomy alone has no role in the treatment of CPP secondary to endometriosis.

Despite its effectiveness in the treatment of endometriosis, limitations of hysterectomy with bilateral oophorectomy include surgical risks, pain recurrence, and the effects of hypoestrogenism. Of women who undergo hysterectomy and bilateral oophorectomy for CPP, 10 percent have recurrent symptoms and 3.7 percent required additional pelvic surgery. Accordingly, a consensus conference recommendation from an expert panel of gynecologists in the United States stated that hysterectomy with bilateral oophorectomy should be reserved for women with symptomatic endometriosis who have completed childbearing and recognize the risk of premature hypoestrogenism, including possible osteoporosis and decreased libido (Gambone, 2002).

APPROACH TO HYSTERECTOMY WITH OOPHORECTOMY

There is no single correct procedure for hysterectomy and bilateral oophorectomy for patients with endometriosis, and surgery may be completed laparoscopically, abdominally, or vaginally (see Section 41-19, Hysterectomy). However, adhesions and distorted anatomy secondary to endometriosis often makes a laparoscopic or vaginal approach more difficult. In addition, the need to remove ovaries may make a vaginal approach less feasible. Accordingly, the choice of procedure will depend on equipment availability, operator experience, and extent of disease.

POSTOPERATIVE HORMONE REPLACEMENT

In response to concerns of increased risk of cardiovascular disease and breast cancer with the use of postmenopausal hormone therapy (HT), attention has been directed toward indiscriminant HT use (Anderson, 2004; Rossouw, 2002). Women with endometriosis who undergo hysterectomy with oophorectomy, however, represent a subset of menopausal women who may be better candidates for HT than women who go through natural menopause. First, women who undergo surgical menopause are usually younger and would likely benefit from replacement of estrogen that is lost by removal of functional ovaries. Estrogen replacement should be considered in women with a surgical menopause for prevention of hypoestrogenic side effects such as hot flashes, osteoporosis, or decreased libido. It has been suggested to treat these women until the time of expected natural menopause, although evidence is lacking.

Although unopposed estrogen may be used in postmenopausal women in the absence of a uterus, disease recurrence has been reported with this therapy in women with severe endometriosis first treated with hysterectomy and oophorectomy (Taylor, 1999). Symptoms required repeat surgery, and did not recur with combined estrogen and a progestin. Additionally, cases of endometrial carcinoma have been reported in women with endometriosis treated with unopposed estrogen after hysterectomy and oophorectomy (Reimnitz, 1988; Soliman, 2004). This is a rare phenomenon and may arise from incompletely resected pelvic endometriosis. Therefore, adding a progestin to the estrogen replacement therapy may be considered in women with severe endometriosis treated surgically.

TREATMENT OF ENDOMETRIOSIS-RELATED INFERTILITY

Medical therapy used for treatment of endometriosis-related pain has not been shown to be effective in increasing fecundity in women with endometriosis (Hughes, 2003). Surgical ablation has been suggested to be beneficial for women with infertility and minimal to mild endometriosis, although the effect was minimal (Marcoux, 1997). Moderate to severe endometriosis may be treated with surgery to restore normal anatomy and tubal function. However, there are no well-designed trials examining the role of

surgery for subfertility in women with severe endometriosis. Alternatively, patients with endometriosis and infertility are candidates for fertility treatments such as controlled ovarian hyperstimulation, intrauterine insemination, and in vitro fertilization (see Chap. 20).

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PELVIC PAIN: INTRODUCTION

Acute and chronic lower abdominal pain are common complaints in office and emergency room settings. However, they vary dramatically by definition, predominant etiologies, and neurophysiology. The mechanisms underlying the perception of pain are not yet fully defined but appear to involve interactions between neurologic, psychological, immunologic, and endocrine factors.

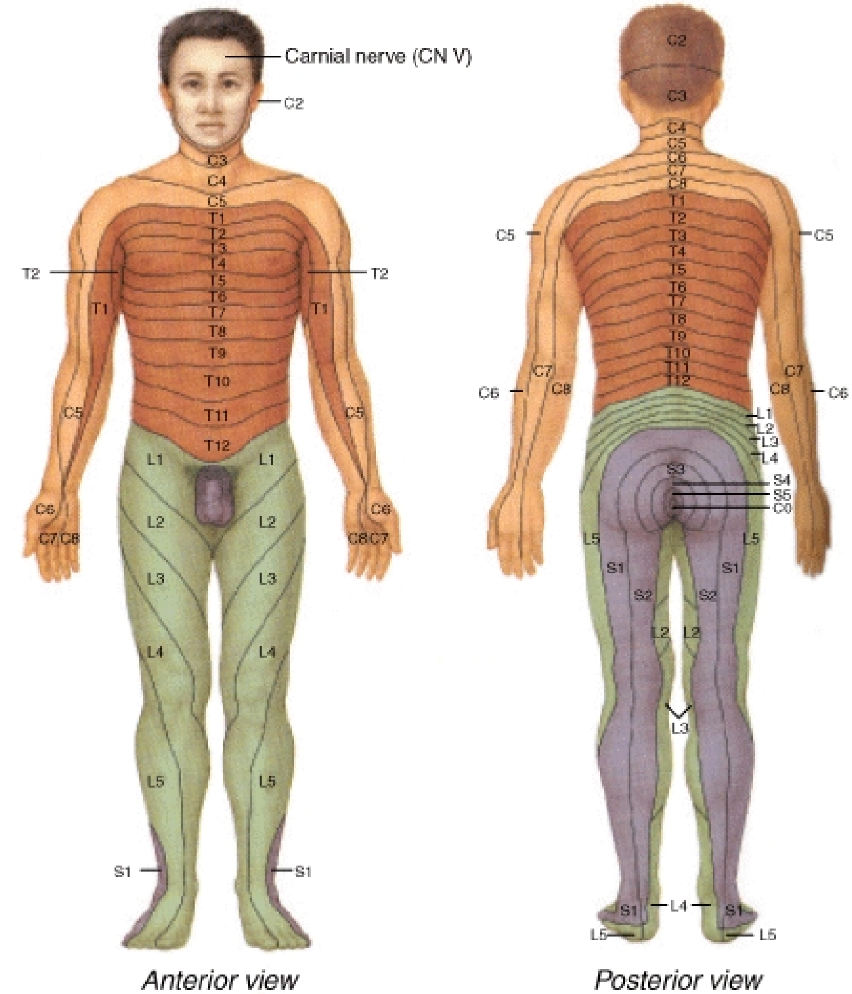
PAIN PATHOPHYSIOLOGY

When categorized, pain may be considered *visceral* or *somatic* depending on the type of afferent nerve fibers involved. Additionally, pain may be described by the neurophysiologic steps that produce it and can be defined as *inflammatory* or *neuropathic* (Kehlet, 2006). Both categorizations are helpful in diagnosing the underlying sources of pain and selecting effective treatment.

Somatic Pain

Somatic pain stems from nerve afferents of the somatic nervous system, which innervates the parietal peritoneum, skin, muscles, and subcutaneous tissues. This pain is typically sharp, localized, and found on either the right or left within dermatomes that correspond to the innervation of involved tissues (Fig. 11-1).

FIGURE 11-1



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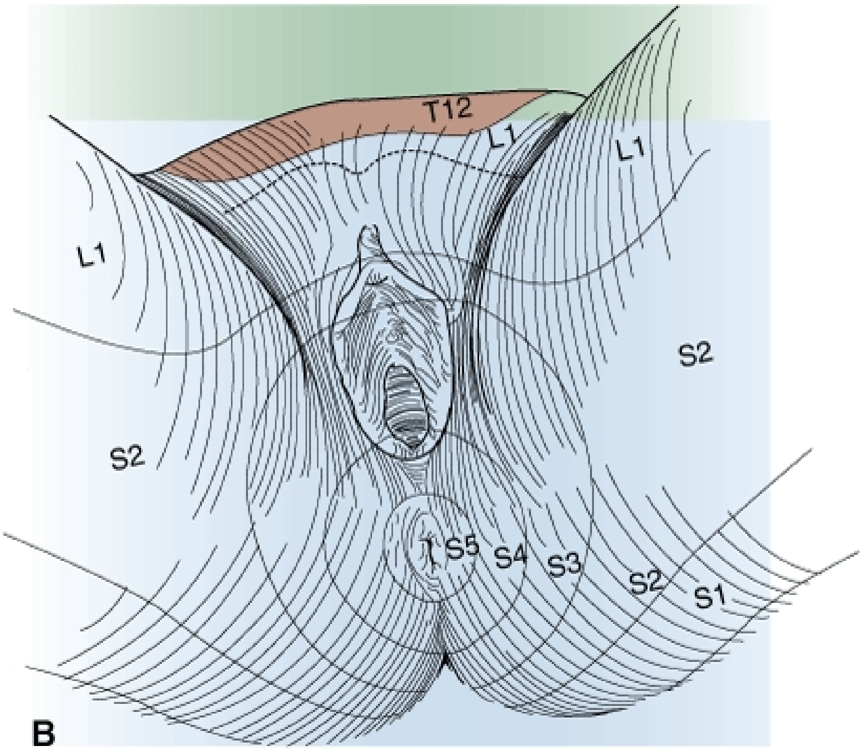
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Dermatome maps. A dermatome is an area of skin supplied by a single spinal nerve. **A.** Body dermatomes. *(From McKinley, 2006, with permission.)* **B.** Perineal dermatomes.

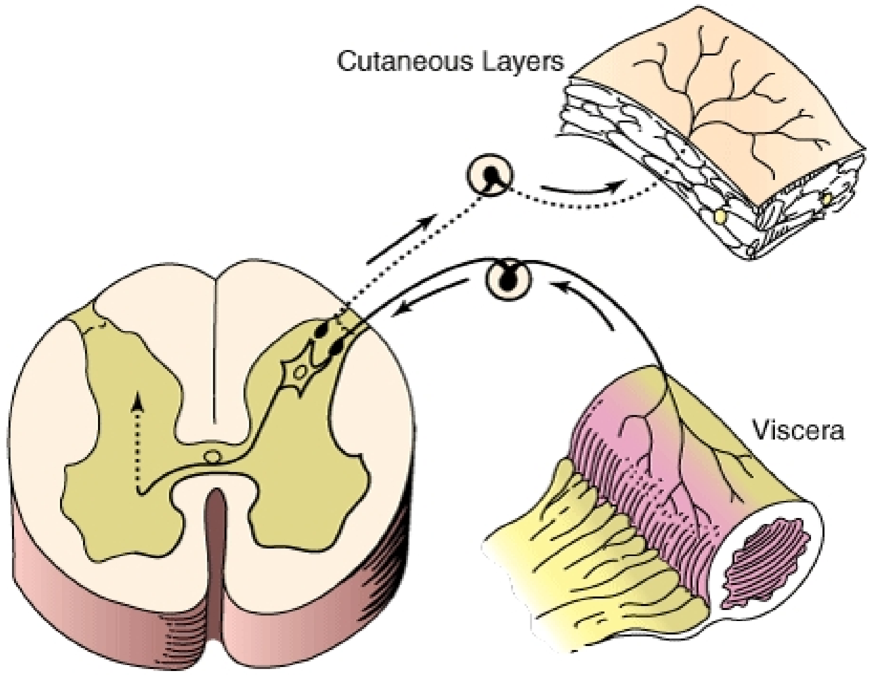
Visceral Pain

Visceral pain stems from afferent fibers of the autonomic nervous system, which transmit information from the viscera and visceral peritoneum. Noxious stimuli typically involve stretching, distension, ischemia, or spasm of abdominal organs. The visceral afferent fibers that transfer these stimuli are sparse, and the resulting diffuse sensory input leads to pain that is often described as a generalized, dull ache.

Visceral pain often localizes to the midline because visceral innervation of abdominal organs is typically bilateral (Flasar, 2006). Visceral afferents follow a segmental distribution, and visceral pain is typically localized by the brain's sensory cortex to an approximate spinal cord level. That level is determined by the embryologic origin of the organ involved. For example, midgut organs, such as the small bowel, appendix, and cecum, cause periumbilical pain. Hindgut organs, such as the colon and intraperitoneal portions of the genitourinary tract, cause pain in the suprapubic or hypogastric area (Gallagher, 2004).

Visceral afferent fibers are poorly myelinated and action potentials may easily spread from them to impact adjacent somatic nerves. As a result, visceral pain may at times be referred to dermatomes that correspond to the impacted somatic nerve fibers (Giamberardino, 2003). In addition, both peripheral somatic and visceral nerves often synapse in the spinal cord at the same dorsal horn neurons. These neurons, in turn, relay sensory information to the brain. The cortex recognizes the signal as coming from the same dermatome regardless of its visceral or somatic nerve origin. This phenomenon, termed *viscerosomatic convergence* , leads to difficulty in a patient distinguishing internal organ pain from abdominal wall or pelvic floor pain (Fig. 11-2) (Perry, 2003).

FIGURE 11-2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Viscerosomatic convergence. Nociceptive impulses originating from a viscera may impact dorsal horn neurons that synapse concurrently with peripheral somatic nerves. These impulses may then be perceived by the brain as coming from a peripheral somatic source rather than the viscera.

Inflammatory Pain

With acute pain, noxious stimuli such as a knife cut, burn, or crush injury activate sensory pain receptors, more formally termed *nociceptors* . Action potentials travel from the periphery to dorsal horn neurons in the spinal cord. Here, reflex arcs may lead to muscle contraction, which immediately removes and protects the body from harm. Additionally within the spinal cord, sensory information is augmented or dampened and may then be transmitted to the brain. In the cortex, it is recognized as pain (Janicki, 2003). After an acute stimulus is eliminated, activity of the nociceptor quickly diminishes.

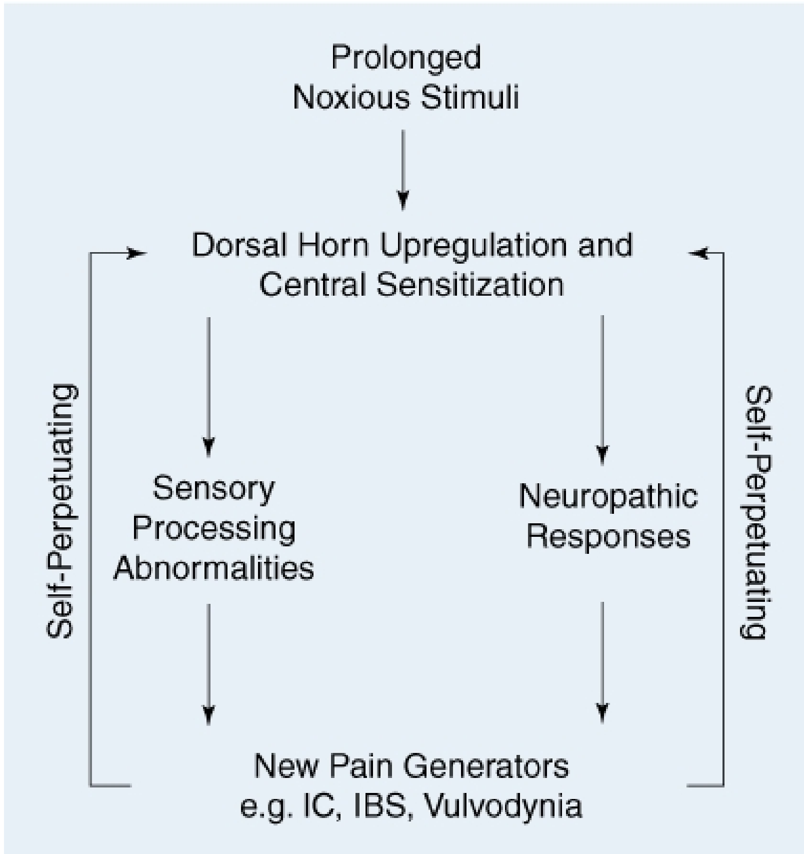
If tissues are injured, then inflammation typically follows. Commonly during an inflammatory process, sensitizing mediators are released into affected tissues and lower the conduction threshold of nociceptors in these tissues. This is termed *peripheral sensitization* . Similarly, neurons within the spinal cord display increased excitability, termed *central sensitization.* As a result, within inflamed tissues, the perception of pain is increased relative to the strength of the external stimulus (Kehlet, 2006).

As inflammation subsides and healing ensues, the increased sensitivity to stimuli and thus the perception of pain resolves.

Neuropathic Pain

In some individuals, sustained noxious stimuli can lead to persistent central sensitization and to a loss of neuronal inhibition that is permanent. As a result, a decreased threshold to painful stimuli remains despite resolution of the inciting stimuli (Butrick, 2003). This persistence characterizes neuropathic pain, which is felt to underlie many chronic pain syndromes (Fig. 11-3). The concept of neuropathic pain helps explain in part why many with chronic pain have pain disproportionately greater to the amount of co-existent disease found.

FIGURE 11-3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Diagram describing theoretical steps required for genesis of chronic pain syndromes. IBS = irritable bowel syndrome; IC = interstitial cystitis. *(Redrawn from Buttrick, 2003, with permission.)*

During central sensitization, neurons within spinal levels above or below those initially affected may eventually become involved. This phenomenon results in chronic pain that may be referred across several spinal cord dermatomes.

Thus, in assessing patients with chronic pain, a clinician may find an ongoing inflammatory condition, in which inflammatory pain dominates. However, for many, pain may be neuropathic. For these, evaluation may ultimately reveal no or minimal current pathology and treatment thus focuses on management of pain symptoms.

ACUTE PAIN

Acute lower abdominal and pelvic pain are common complaints. The definition of these varies based on duration, but in general, discomfort is present less than 7 days. The sources of acute lower abdominal and pelvic pain are extensive and a thorough history and physical examination can aid in narrowing the list (Table 11-1).

Table 11-1 Etiologies of Acute Lower Abdominal and Pelvic Pain

Periumbilical
Appendicitis (early)
Small bowel obstruction

Gastroenteritis Mesenteric ischemia Abdominal aortic aneurysm rupture Abdominal aortic aneurysm dissection
Right lower quadrant Appendicitis Inflammatory bowel disease Ovarian tumor Ovarian torsion Ectopic pregnancy Pelvic inflammatory disease Tubo-ovarian abscess Pyelonephritis Perinephric abscess Urolithiasis Gastrointestinal malignancy Right-sided diverticulitis Ileocolitis Gastroenteritis Hernia
Suprapubic Irritable bowel disease Ovarian tumor Ovarian torsion Ectopic pregnancy Pelvic inflammatory disease Tubo-ovarian abscess Dysmenorrhea Colonic disease Diverticulitis Cystitis Nephrolithiasis
Left lower quadrant Irritable bowel disease

Ovarian tumor Ovarian torsion Ectopic pregnancy Pelvic inflammatory disease Tubo-ovarian abscess Pyelonephritis Perinephric abscess Nephrolithiasis Sigmoid diverticulitis Ileocolitis Gastroenteritis Hernia Gastrointestinal malignancy
Diffuse Gastroenteritis Bowel obstruction Peritonitis Mesenteric ischemia Irritable bowel disease Diabetic ketoacidosis Porphyria Uremia Hypercalcemia Sickle cell crisis Vasculitis Heavy metal intoxication Opiate withdrawal Familial Mediterranean fever Hereditary angioedema

Modified from Flasar, 2006, with permission.

Diagnosis

HISTORY

In addition to a thorough medical and surgical history, a verbal description of the pain and its associated factors is essential. For example, duration can be informative, and pain with abrupt onset may be more often associated with organ torsion, rupture, or

ischemia.

Moreover, the nature of pain may add value. Patients with visceral pathology may describe midline pain that is diffuse, dull, achy, or cramping. They may repeatedly shift or roll to one side to find a comfortable position.

If the underlying pathology stems from infection or necrosis, then inflammation of the adjacent parietal peritoneum may create a sharp pain that is localized to a corresponding dermatome. Alternatively, such sharp, localized pain may also involve pathology of specific muscles or isolated areas of skin or subcutaneous tissues. In either instance, with somatic pain, patients classically rest motionless to avoid movement of the affected peritoneum, muscle, or skin.

Colicky pain may reflect bowel obstructed by adhesion, neoplasia, stool, or hernia, or may result from increased bowel peristalsis in those with irritable or inflammatory bowel disease or infectious gastroenteritis. Alternatively, forceful uterine contractions with the passage of products of conception, pedunculated submucous leiomyomas, or endometrial polyps may create colic. In addition, stones in the lower urinary tract may cause spasms of pain as they are passed.

Associated symptoms may also direct diagnosis. For example, absence of dysuria, hematuria, frequency, or urgency will exclude urinary pathology in most instances. Gynecologic causes are often associated with vaginal bleeding, vaginal discharge, dyspareunia, or amenorrhea. Alternatively, exclusion of diarrhea, constipation, or gastrointestinal bleeding lowers the probability of gastrointestinal (GI) disease.

Vomiting complaints, however, are less informative. However, the temporal relationship of vomiting to the pain may be helpful. In the surgical abdomen, if vomiting is present it usually follows as a response to pain and is a result of vagal stimulation. This vomiting is typically severe and occurs without nausea. Conversely, if vomiting is noted prior to pain or concurrent with it, a surgical abdomen is less likely (Miller, 2006).

In general, well-localized pain or tenderness persisting for longer than 6 hours and unrelieved by analgesics, has an increased likelihood of acute peritoneal pathology.

PHYSICAL EXAMINATION

Vital Signs

Initial examination begins with assessment of a woman's general appearance, including facial expression, diaphoresis, pallor, and degree of agitation. Vital signs are assessed, and elevated temperature, tachycardia, and hypotension should prompt an expedited evaluation, as the risk for intra-abdominal pathology increases with their presence. Constant low-grade fever is common in inflammatory conditions such as diverticulitis and appendicitis, and higher temperatures may be seen with pelvic inflammatory disease (PID), advanced peritonitis, or pyelonephritis.

Pulse and blood pressure evaluation should assess orthostatic changes if intravascular hypovolemia is suspected. A pulse increase of 30 beats per minute or a systolic blood pressure drop of 20 mm Hg or both, between lying and standing after 1 minute, is often reflective of hypovolemia. If noted, establishment of intravenous access and rehydration may be required prior to completion of the examination. However, certain neurologic disorders and medications, such as tricyclic antidepressants or antihypertensives may also produce similar orthostatic blood pressure changes (Saperston, 2004).

Abdominal Examination

Visual inspection of the abdomen focuses on prior surgical scars, which may increase the possibility of bowel obstruction from postoperative adhesions or incisional hernia. Additionally, abdominal distension may be seen with bowel obstruction, perforation, or ascites. After inspection, auscultation of the abdomen may identify hyperactive or high-pitched bowel sounds characteristic of bowel obstruction. Hypoactive sounds, however, provide less diagnostic information.

Palpation of the abdomen should systematically explore each abdominal quadrant and begin away from the area of indicated pain. Peritoneal irritation is suggested by rebound tenderness or by abdominal rigidity due to involuntary guarding or reflex spasm of the abdominal muscles.

Pelvic Examination

In general, pelvic examination should be performed in reproductive-aged women, as gynecologic pathology and complications of pregnancy are a common cause of pain in this age group. The decision to proceed with this examination in geriatric and pediatric patients may be based on clinical information.

Of findings, purulent vaginal discharge or cervicitis may reflect PID (see Chap. 3, Pelvic Inflammatory Disease). Vaginal bleeding may stem from pregnancy complications, benign or malignant reproductive tract neoplasia, or acute vaginal trauma (see Chap. 8). Pregnancy, leiomyomas, and adenomyosis are common causes of uterine enlargement, and the former two may also create uterine softening (see Chap. 9, Uterus). Cervical motion tenderness is commonly associated with peritoneal irritation and may be seen with PID, appendicitis, diverticulitis, and intra-abdominal bleeding. A tender adnexal mass may reflect ectopic pregnancy, tubo-ovarian abscess, or ovarian cyst with torsion, hemorrhage, or rupture. Alternatively, a tender mass may reflect an abscess involving the appendix or colon diverticulum. Rectal examination can add additional information regarding the source and size of pelvic masses as well as the possibility of colorectal pathologies. Stool guaiac testing for occult blood, although less sensitive when not performed serially, is still warranted in many cases (Rockey, 2005).

In emergency room settings, women with acute pain may experience waits between an initial assessment and laboratory testing, specialist consultation, or radiologic imaging. For these patients, recent literature supports early administration of analgesia. Fears that analgesia will mask patient symptoms and hinder accurate diagnosis have not been supported (McHale, 2001; Pace, 1996). Thus, barring significant hypotension or drug allergy, morphine sulfate may be administered and increased as needed in these situations.

LABORATORY TESTING

Despite benefits from a thorough history and physical examination, the sensitivity of these two in diagnosing abdominal pain is low (Gerhardt, 2005). Thus, laboratory and diagnostic testing are typically required. In women with acute abdominal pain, complications of pregnancy are common. Thus, either urine or serum β-hCG testing is recommended in those of reproductive age without a history of hysterectomy. Complete blood count (CBC) can aid in assessment of hemorrhage, both vaginal and intra-abdominal, and assess the possibility of infection. Urinalysis may be used to evaluate possible urolithiasis or cystitis. In addition, microscopic evaluation and culture of vaginal discharge can add support to clinically suspected cases of PID.

RADIOLOGIC IMAGING

In women with acute pelvic pain, sonography is commonly used (Lambert, 2004; Okaro, 2004). In most cases, a transvaginal approach offers superior resolution of reproductive organs. However, if pelvic organs are significantly large and lie outside the true pelvis, transabdominal sonography may be necessary to image entire structures. Moreover, in cases in which sonographic findings are equivocal or nondiagnostic, computed tomography (CT) is widely used for its ability to detect a great variety of bowel, reproductive tract, and urinary disorders (Leschka, 2005). Computed tomography has superior sensitivity compared with abdominal radiography. Thus, many advocate it as a primary tool in settings in which radiography would be ordered, such as with suspected bowel obstruction, perforation, or generalized nontraumatic abdominal pain (Ahn, 2002; MacKersie, 2005).

LAPAROSCOPY

Operative laparoscopy is the primary treatment for appendectomy, ovarian torsion, and for ruptured tubal ectopic pregnancy or ruptured ovarian cyst associated with symptomatic hemorrhage. Moreover, diagnostic laparoscopy may be useful if no pathology can be identified by conventional diagnostics. However, in stable patients with acute abdominal pain, noninvasive testing is typically fully exhausted before considering this approach (Sauerland, 2006).

CHRONIC PAIN

Persistent pain symptoms in women may take several forms and include dysmenorrhea, dyspareunia, chronic pelvic pain (CPP), musculoskeletal pain, intestinal cramping, or dysuria. The list of pathologies that may underlie these chronic pain symptoms is extensive and includes both psychological and organic disorders (Table 11-2). Moreover, pathology in one organ can commonly lead to dysfunction in adjacent systems. As a result, a woman with chronic pain may have more than one cause of pain and overlapping symptoms. Thus, a comprehensive evaluation of multiple organ systems and psychological state is essential for complete treatment.

Table 11-2 Diseases that May Be Associated with Chronic Pelvic Pain in Women
Gynecologic
Extrauterine
Adhesions
Adnexal cysts
Chronic ectopic pregnancy
Chlamydial endometritis or salpingitis
Endometriosis
Endosalpingiosis
Neoplasia of the genital tract
Ovarian retention syndrome (residual ovary syndrome)
Ovarian remnant syndrome
Ovulatory pain
Postoperative peritoneal cysts
Residual accessory ovary
Subacute salpingo-oophoritis (chronic PID)
Uterine
Adenomyosis
Atypical dysmenorrhea or ovulatory pain
Cervical stenosis
Chronic endometritis
Endometrial or endocervical polyps
Intrauterine contraceptive device
Leiomyomas
Symptomatic pelvic floor relaxation
Urologic
Bladder neoplasm
Chronic urinary tract infection

Detrusor dysynergia
Interstitial cystitis
Radiation cystitis
Recurrent acute cystitis or urethritis
Stone/urolithiasis
Urethral diverticulum
Gastrointestinal
Carcinoma of the colon
Chronic intermittent bowel obstruction
Colitis
Constipation
Diverticular disease
Inflammatory bowel disease
Irritable bowel syndrome
Musculoskeletal
Abdominal wall myofascial pain
Coccydynia
Compression of lumbar vertebrae
Degenerative joint disease
Disk herniation or rupture
Faulty or poor posture
Fibromyositis
Hernias: ventral, inguinal, femoral, spigelian
Levator ani syndrome
Low back pain
Muscular strains and sprains
Neoplasia of spinal cord or sacral nerve
Neuralgia of iliohypogastric, ilioinguinal, and/or genitofemoral nerves

Piriformis syndrome
Rectus tendon strain
Spondylosis
Other
Abdominal cutaneous nerve entrapment
Familial Mediterranean fever
Neurologic dysfunction
Porphyria
Psychiatric disorders
Shingles

PID = pelvic inflammatory disease.

Modified from Howard, 2003, with permission.

Chronic Pelvic Pain

Chronic pelvic pain is a common gynecologic problem and Mathias (1996) estimated its prevalence in reproductive-aged women at 15 percent. There is no universally accepted definition of chronic pelvic pain. However, many investigators distinguish it from dysmenorrhea and dyspareunia and define it as noncyclic pain that persists for 6 or more months; localizes to the pelvis, infraumbilical anterior abdominal wall, or lumbosacral back or buttocks; and leads to degrees of functional disability (American College of Obstetricians and Gynecologists, 2004).

ETIOLOGY

Causes of chronic pelvic pain fall within a broad spectrum, but endometriosis, symptomatic leiomyomas, interstitial cystitis, and irritable bowel syndrome are commonly diagnosed. Diagnosis and treatment of pain related to endometriosis is discussed fully in Chapter 10, Patient Symptoms. Evaluation and management of chronic pain secondary to leiomyomas is found in Chapter 9, Pelvic Discomfort and Dysmenorrhea.

The pathophysiology of CPP is unclear in many cases and may have a significant association with neuropathic pain described earlier (Neuropathic Pain). Chronic pelvic pain shows increased association with irritable bowel syndrome, interstitial cystitis, and vulvodynia. These are also considered by many to be chronic visceral pain syndromes stemming from neuropathic pain (Janicki, 2003).

HISTORY

More than with many other gynecologic complaints, a detailed history and physical examination is integral to diagnosis. A pelvic pain questionnaire can be used initially to obtain information. One example is available from the International Pelvic Pain Society and may be downloaded free of charge at http://www.pelvicpain.org/pdf/FRM_Pain_Questionnaire.pdf . At minimum, the series of questions found in Table 11-3 may provide valuable information.

Table 11-3 Brief Historical Survey in the Evaluation of Chronic Pelvic Pain

1. How old are you?
2. How many pregnancies have you had?
3. Where does it hurt?
4. How much does it hurt?
5. What is the quality or character of your pain?
6. Do you have pain with your periods?
7. Does your pain worsen with menses or just before menses?
8. Is there any cyclic pattern to your pain? Is it the same 24 hours a day, 7 days a week?
9. Is your pain constant or intermittent?
10. When and how did your pain start and how has it changed?
11. Did pain start initially as menstrual cramps (dysmenorrhea)?
12. What makes your pain better?
13. What makes your pain worse?
14. Do you have pain with deep penetration during intercourse? If so, does it continue afterwards?
15. Have you ever been diagnosed with or treated for a sexually transmitted disease or pelvic inflammatory disease?
16. What form of birth control do you use and have you used in the past?
17. Have you ever had any kind of surgery?
18. What prior evaluations or treatments have you had for your pain? Have any of the previous treatments helped?
19. How has the pain affected your quality of life?
20. Are you depressed or anxious?
21. Are you taking any drugs?
22. Have you been or are you now being abused physically or sexually? Are you safe?
23. What other symptoms or health problems do you have?
24. What do you believe or fear is the cause of your pain?

From Howard, 2003, with permission.

Obstetric History

Pregnancy and delivery can be traumatic to neuromuscular structures and have been linked with pelvic organ prolapse, pelvic floor muscle myofascial pain syndromes, and symphyseal or sacroiliac joint pain. In addition, injury to the ilioinguinal or iliohypogastric nerves during Pfannenstiel incision for cesarean delivery may lead to lower abdominal wall pain even years after the initial injury (Whiteside, 2003). Alternatively, in a nulliparous woman with infertility, pain may stem from endometriosis, pelvic adhesions, or pelvic inflammatory disease.

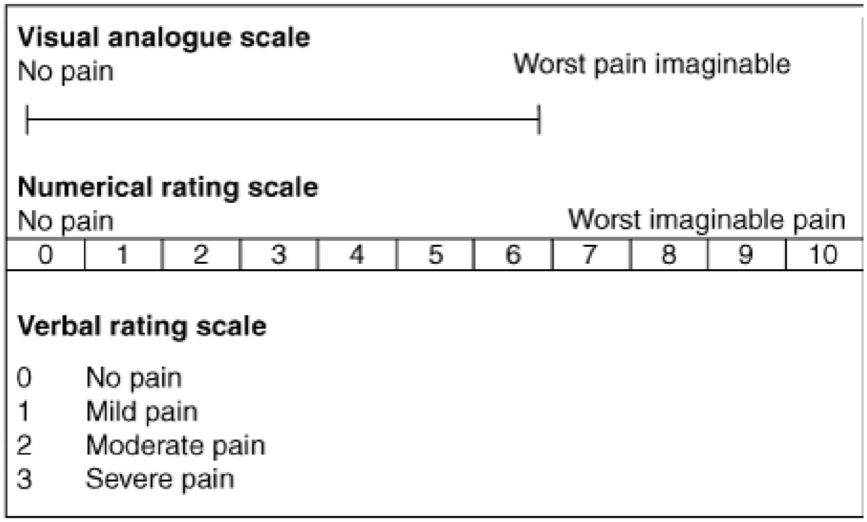
Surgical History

Prior abdominal surgery increases a woman's risk for pelvic adhesions, especially if infection, bleeding, or large areas of denuded peritoneal surfaces were involved. In addition, certain disorders persist or commonly recur, and thus information regarding prior surgeries for endometriosis, adhesive disease, or malignancy should be sought.

Pain Characteristics

Various pain scales improve the assessment of pain, and the Visual Analog Scale (VAS), Verbal Descriptor Scales (VDS), and McGill Pain Questionnaire and Short Form (MPQ, MPQ-SF) are commonly used to measure pain intensity (Figs. 11-4 and 11-5) (Herr, 2004). In addition, questions pertaining to pain duration, aggravating and relieving factors, and timing during the day and menstrual cycle are valuable. For example, if a woman notes the combination of dysmenorrhea, CPP, and dyspareunia, the risk of finding endometriosis at laparoscopy is threefold that in women with no symptoms (Fedele, 1992).

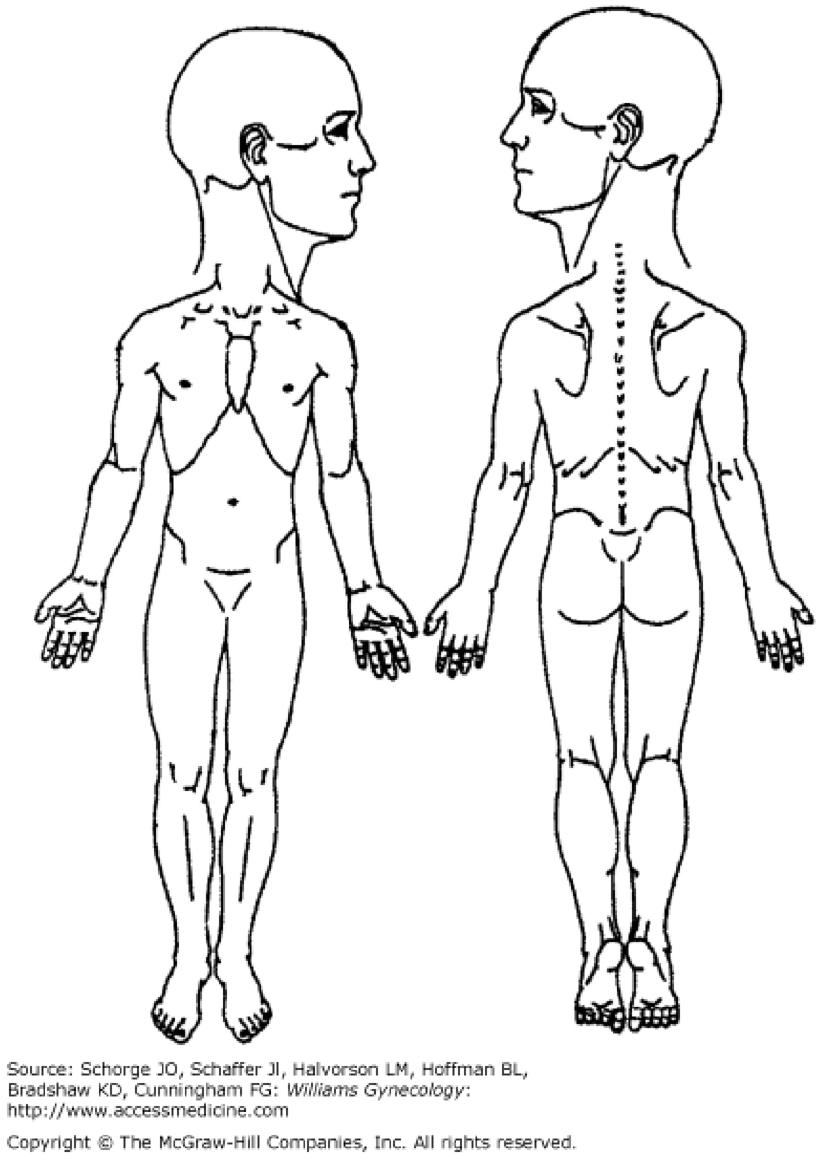
FIGURE 11-4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Visual analogue numerical, verbal rating scales.

FIGURE 11-5



Short Form McGill Pain Diagram. Patient should mark sites and intensities of pain. *(Â©Copyright 1970, 1984, 1987. Reprinted with permission from D.R. Melzack.)*

Psychosocial History

There is a significant association between physical, emotional, or sexual abuse and chronic pelvic pain (Bodden-Heidrich, 1999; Jamieson, 1997; Lampe, 2000). Additionally, for some women, chronic pain is an acceptable means to cope with social stresses. For these reasons, patients should be questioned about domestic violence and satisfaction with family relationships. Furthermore, an inventory of depressive symptoms is essential, as depression may cause or result from chronic pelvic pain (see Table 13-5).

PHYSICAL EXAMINATION

The etiology of chronic pain is varied and information gathered from physical examination can often clarify the source and direct further testing. In a woman with chronic pain, examination may be painful. For example, in those with neuropathic pain, mere light touch may elicit pain, which is termed *allodynia* . Therefore, the patient's ability to halt evaluation at any time should be understood. Examination should proceed slowly to allow relaxation between each step.

Stance and Gait

Women with intraperitoneal pathology may compensate with changes in posture, and such adjustments can create secondary musculoskeletal sources of pain (Musculoskeletal). Alternatively, musculoskeletal structures may be the site of referred pain from these organs (Table 11-4). Thus, orthopedic evaluation is integral in the evaluation of women with chronic pelvic pain.

Table 11-4 Musculoskeletal Origins of Chronic Pelvic Pain

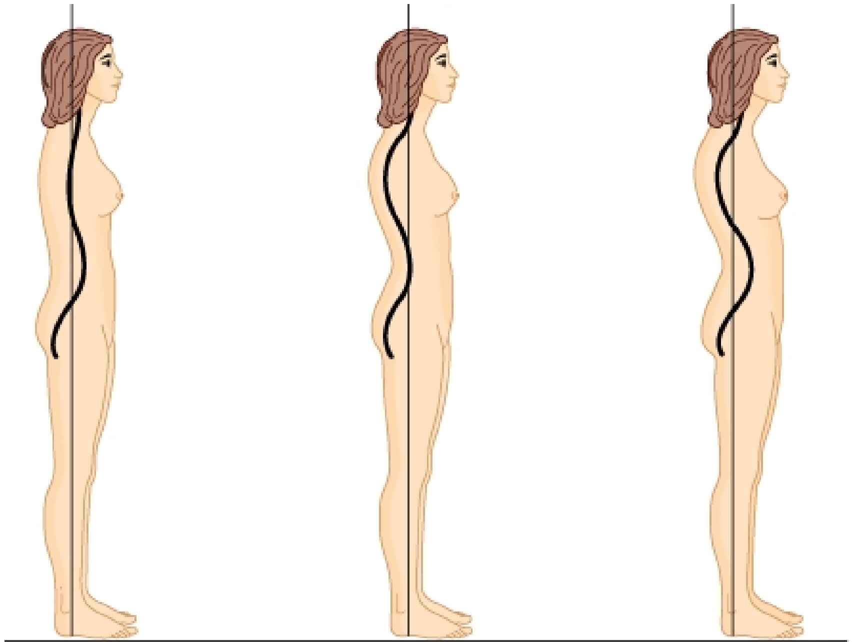
Structure	Innervation	Referred Pain Site(s)
Hip	T12â€"S1	Lower abdomen; anterior medial thigh; knee
Lumbar ligaments, facets/disks	T12â€"S1	Low back; posterior thigh and calf; lower abdomen; lateral trunk; buttock
Sacroiliac joints	L4â€"S3	Posterior thigh; buttock; pelvic floor
Abdominal muscles	T5â€"L1	Abdomen; anteromedial thigh; sternum
Pelvic and back muscles		
Iliopsoas	L1â€"L4	Lateral trunk; lower abdomen; low back; anterior thigh
Piriformis	L5â€"S3	Low back, buttock; pelvic floor
Pubococcygeus	S1â€"L4	Pelvic floor; vagina; rectum; buttock
Obturator internal/external	L3â€"S2	Pelvic floor; buttock; anterior thigh
Quadratus lumborum	T12â€"L3	Anterior lateral trunk; anterior thigh; lower abdomen

Modified from Baker, 1993, with permission.

Initially, a woman is examined while standing. Posture should be evaluated anteriorly, posteriorly, and laterally. Posterior, inspection for scoliosis and levelness of the shoulders, gluteal folds, and knee creases is performed. Asymmetry may reflect musculoskeletal disorders.

Lateral visual examination may reveal lordosis and concomitant kyphosis, which has been noted in some women with CPP and termed *typical pelvic pain posture* (TPPP) (Fig. 11-6) (Baker, 1993). Abnormal tilt of the pelvic bones can be assessed by simultaneously placing an open palm on each side between the PSIS and anterior superior iliac spine (ASIS). Normally, the ASIS lies one-quarter inch below the level of the PSIS and greater distances may suggest abnormal tilt. Pelvic tilt may be associated with hip osteoarthritis and other orthopedic problems (Labelle, 2005; Yoshimoto, 2005).

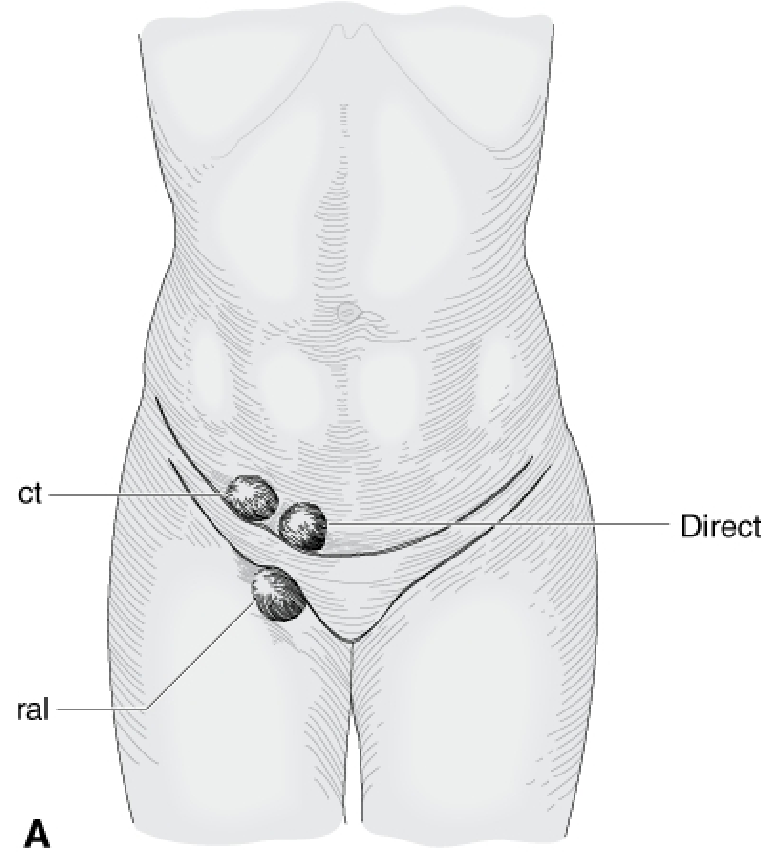
FIGURE 11-6



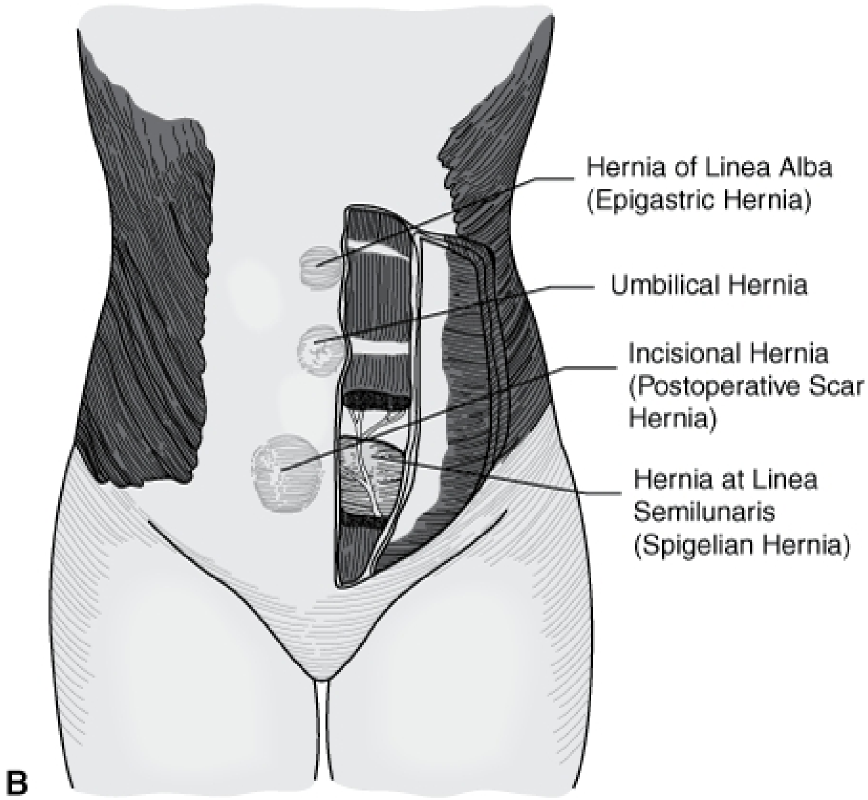
Postural changes associated with lordosis and kyphosis-lordosis. TPPP = typical pelvic pain posture. *(From Howard, 2000, with permission.)*

Anterior inspection should focus on symmetry of the ASISs, umbilicus, and weight bearing. If one leg is dominant in weight bearing, the nonbearing leg is often externally rotated and slightly flexed at the knee. In addition to carriage, the anterior abdominal wall should additionally be inspected for signs of hernia (Fig. 11-7). Those that involve the anterior abdominal wall and pelvic floor are most commonly associated with CPP. Less frequently, *sciatic hernia,* which is herniation of peritoneum and peritoneal contents through the greater sciatic foramen, and *obturator hernia,* which is that through the obturator canal, have also been described sources of pain (Chang, 2005; Miklos, 1998; Moreno-Egea, 2006; Servant, 1998).

FIGURE 11-7



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

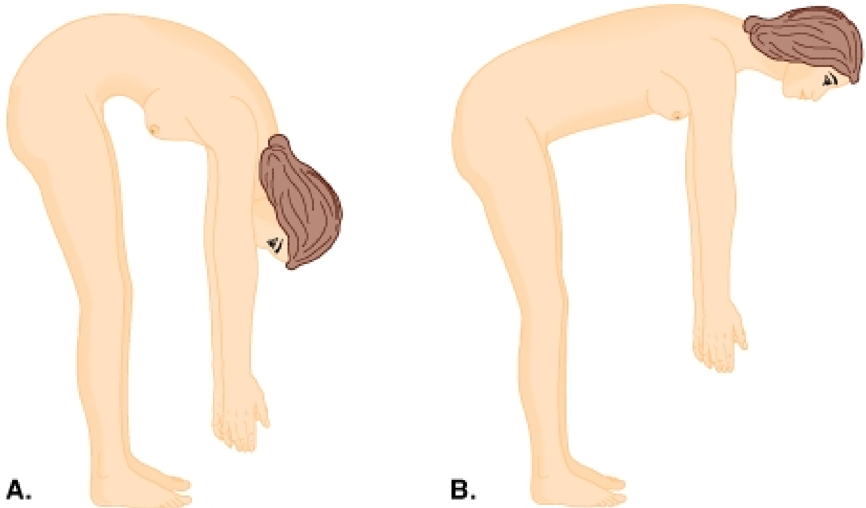


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Hernia types. **A.** Inguinal and femoral hernias. *(From Howard, 2000, with permission.)* **B.** Hernias that may involve the anterior abdominal wall. *(From Carter, 2000, with permission.)*

Mobility limitations may also be informative. A patient should be asked to bend forward at the waist. Limitation in forward flexion may reflect primary orthopedic disease or adaptive shortening of back extensor muscles, which is seen frequently in women with chronic pain and TPPP (Fig. 11-8). In such cases, patients are unable to create the normal convex curve with this motion.

FIGURE 11-8

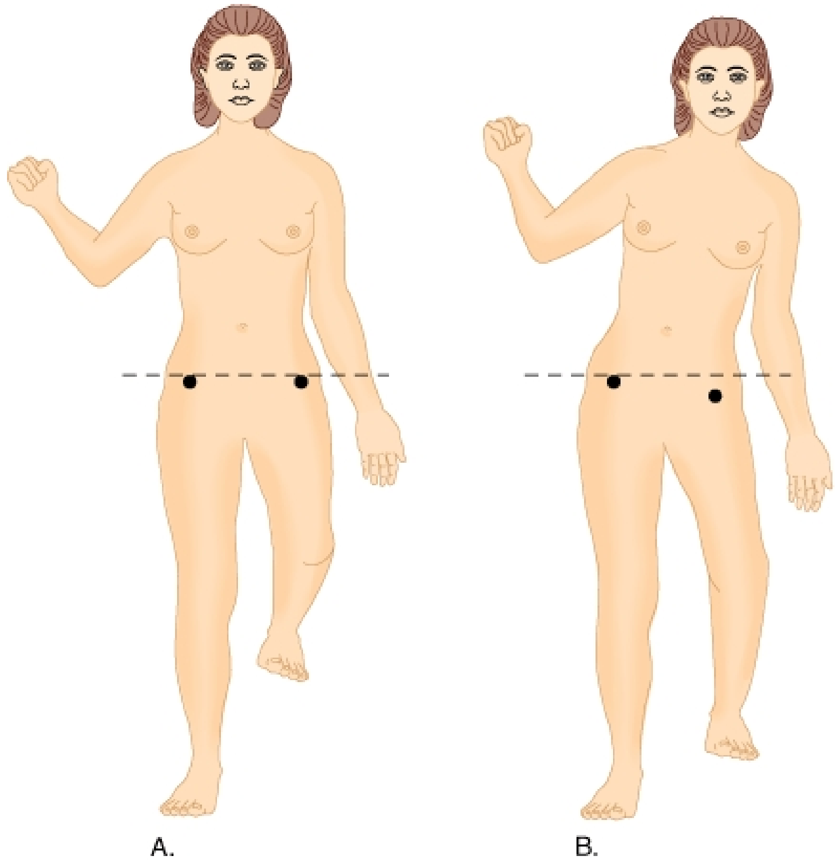


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Mobility testing. **A.** Normal flexion. **B.** Limited flexion may be seen in those with orthopedic disease or in those with chronic pelvic pain. *(From Baker, 1998, with permission.)*

Muscle weakness may also indicate orthopedic disease. A Trendelenburg test, in which a patient is asked to balance on one foot, can indicate dysfunction of hip abductor muscles or hip joint. With a positive test, when a woman elevates a leg by flexing the hip, the ipsilateral iliac crest droops (Fig. 11-9).

FIGURE 11-9



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Trendelenburg test. **A.** In women without orthopedic disease, hip levels remain equal with leg lifting. **B.** Dropping of the nonweightbearing leg is a positive test and may indicate hip muscle or joint disease. *(From Baker, 1998, with permission.)*

Gait may also be evaluated. An *antalgic gait,* known as a limp, refers to a posture or gait that minimizes weight bearing on a lower limb or joint and indicates a higher probability of musculoskeletal pain.

Supine

The anterior abdominal wall should be evaluated for abdominal scars, which might serve as sites of hernia or nerve entrapment or may indicate intra-abdominal adhesive disease. Auscultation for bowel sounds and bruits should follow. Increased bowel activity may reflect irritable or inflammatory bowel diseases. Bruits should prompt investigation for vascular pathology.

While supine, a woman is asked to demonstrate with one finger the point of maximal pain and then encircle the total surrounding area of involvement. Superficial palpation of the anterior abdominal wall by a clinician may reveal sites of tenderness or knotted muscle that may reflect nerve entrapment or myofascial pain syndromes (Musculoskeletal). Moreover, pain with elevation of the head and shoulders while tensing the abdominal wall muscles, *Carnett sign,* is typical of anterior abdominal wall pathology. Tenderness originating from inside the abdominal cavity usually decreases with this test (Thomson, 1991). In addition, Valsalva maneuver during head and shoulder elevation may display diastasis of the rectus abdominis muscle or hernias. Diastasis recti can be differentiated in most cases from a ventral hernia. With diastasis, the borders of the rectus abdominis muscle can be palpated bilaterally along the entire length of the protrusion.

Deep palpation of the lower abdomen may identify pathology originating from pelvic viscera. Specifically, tenderness at the junction of the upper and middle thirds of a line drawn between the symphysis and anterior superior iliac spine may indicate pelvic congestion syndrome (Pelvic Congestion Syndrome). Dullness to percussion or a shifting fluid wave may reflect ascites.

Tests of mobility may give additional information. In most cases, a woman can elevate her leg 80Â° from the horizontal toward her head, termed a *straight leg test.* Pain with leg elevation may be seen with lumbar disk, hip joint, or myofascial pain syndromes. Additionally, symphyseal pain with this test may indicate laxity in the symphysis pubis or pelvic girdle. Both the obturator and iliopsoas tests may indicate myofascial pain syndromes involving these muscles or disorders of the hip joint. With the obturator test, a supine patient brings one thigh into 90Â° of flexion while the foot remains planted. The ankle is immobilized and the knee is gently pulled laterally and then medially to assess for tenderness. With the iliopsoas test, a supine woman attempts to flex each thigh separately against resistance from the examiner's hand. If pain is described with flexion, the test result is positive.

Sitting

A patient's posture in the sitting position should be inspected. Myofascial pain syndromes involving pelvic floor muscles often lead to patients shifting weight to one buttock or sitting toward a chair's front edge.

Lithotomy

Pelvic examination should begin with inspection of the vulva for generalized changes and localized lesions as outlined in Chapter 4. Specifically, erythema may reflect vulvitis or chronic fungal infection. Alternatively, thinning of vulvar skin may result from lichen sclerosus or atrophic changes.

After inspection, systematic pressure point palpation of the vulva is completed with a small cotton swab to map areas of pain (see Fig. 4-11). Palpation of the vagina ideally begins with one finger, which is gradually inserted 3 to 4 cm. Systematic sweeping pressure against the pelvic floor muscles along their length may identify isolated knots of taut muscle in those with myofascial pain syndrome of the pelvic floor. Typically, the pubococcygeus, iliococcygeus, and obturator intemus muscles can be reached with a vaginal finger (see Fig. 38-6). Additionally, tenderness of the urethra and bladder are potential indicators of urethral diverticulum or interstitial cystitis, respectively. Pain with deep palpation of the vaginal fornices may be seen with endometriosis, and cervical motion tenderness may be noted with PID. If pain follows gentle movement of the coccyx, then articular disease of the coccyx, termed *coccydynia,* is suspected.

Assessment of the uterus may reveal an enlarged uterus from leiomyomas, whereas enlargement with softening is more typical of adenomyosis. Immobility of the uterus may follow scarring from endometriosis, PID, malignancy, or adhesive disease from prior surgeries. Evaluation of the adnexa may reveal tenderness or mass. Such lateral tenderness may reflect endometriosis, diverticular disease, or pelvic congestion syndrome.

Rectal examination and rectovaginal palpation of the rectovaginal septum should be included. Palpation of hard stool or hemorrhoids may indicate GI disorders, whereas nodularity of the rectovaginal septum may be found with endometriosis or neoplasia. Myofascial tenderness involving the puborectalis and coccygeus muscles may be noted by sweeping the index finger with pressure across these muscles. Lastly, stool guaiac testing may be performed at the initial visit, or a woman may be sent home with serial guaiac testing cards to complete.

TESTING

Laboratory Evaluation

For women with chronic pelvic pain, diagnostic testing may add valuable information. Results from urinalysis and urine culture may indicate urinary tract stones, malignancy, or recurrent infection as sources of pain. Thyroid disease can affect physiologic functioning and may be found in those with bowel or bladder symptoms. Thus, serum thyroid-stimulating hormone (TSH) levels are commonly assayed. Diabetes can lead to neuropathy, and screening may be completed with urinalysis or serum evaluation.

Radiologic Imaging and Endoscopy

These modalities may be informative, and of these, transvaginal sonography is widely used by gynecologists to evaluate chronic pelvic pain. Sonography of the pelvic organs may reveal endometriomas, leiomyomas, ovarian cysts, and other structural lesions. However, despite its applicability for many gynecologic pathologies, sonography has poor sensitivity in identifying endometriotic implants or adhesions. Similarly, CT or MR imaging may be used, but often adds little additional information to that obtained with sonography.

In those with bowel symptoms, barium enema may indicate internal or external obstructive lesions, malignancy, and diverticular or inflammatory bowel disease. However, flexible sigmoidoscopy and colonoscopy may offer more information because colonic mucosa can be directly inspected and biopsied if necessary. In those in whom pelvic congestion syndrome is suspected, pelvic venography is the primary tool. This technique requires cannulation of the femoral vein to access the internal iliac vessels for contrast injection (Diagnosis).

Cystoscopy, laparoscopy, flexible sigmoidoscopy, and colonoscopy may each be employed, and patient symptoms will dictate their use. In those with symptoms of chronic pain and urinary symptoms, cystoscopy is typically advised. If gastrointestinal complaints are dominant, then flexible sigmoidoscopy or colonoscopy may be warranted. For many women with no obvious cause of their CPP, laparoscopy is performed, and approximately 40 percent of all gynecologic laparoscopies are performed for this indication (Howard, 1993). Importantly, intraoperative explanations for CPP are commonly found in those with normal preoperative examinations (Cunanan, 1983; Kang, 2007). Laparoscopy allows direct identification, and in many cases, treatment of intra-abdominal pathology.

One newer laparoscopic approach to CPP is performed under local anesthesia with the patient conscious and available for questioning regarding sites of pain (Howard, 2000; Swanton, 2006). Termed *conscious pain mapping,* this technique has resulted in improved postoperative pain scores but its clinical use to date has been limited.

TREATMENT

In many women with CPP, an identifying source is found and treatment is dictated by the diagnosis. However, in other cases, pathology may not be identified and treatment is directed toward dominant symptoms.

Analgesics

Treatment of pain typically begins with oral analgesics such as acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) (see Table 10-2). These are particularly helpful if inflammatory states underlie the pain.

If satisfactory relief is not achieved, then a mild opioid such as codeine or hydrocodone may be added to this regimen. Opioids are most effective and least addictive if given on a scheduled basis and at doses that adequately relieve pain (Table 39-15). If pain persists, stronger opioids such as morphine, methadone, fentanyl, oxycodone, and hydromorphone can replace milder ones. Close and regular surveillance is essential (Gunter, 2003).

Hormonal Suppression

Endometriosis is a common disorder found in women with CPP. Hormonal suppression may be considered, especially in those with co-existent dysmenorrhea or dyspareunia and who lack dominant bladder or bowel symptoms. As discussed in Chapter 10, Diagnostic Algorithm, combination oral contraceptives, progestins, gonadotropin-releasing hormone (GnRH) agonists, and certain androgens have proven effective.

Antidepressants and Anticonvulsants

For many, CPP represents neuropathic pain, and therapy has been extrapolated from treatment of such pain in other disorders. Tricyclic antidepressants have repeatedly been shown to reduce neuropathic pain independent of their antidepressant effects (Saarto, 2005). Moreover, antidepressants are a logical choice, as clinically significant depression is commonly comorbid with pain. Amitriptyline (Elavil) and its metabolite nortriptyline (Pamelor) have the best documented efficacy in the treatment of neuropathic and non-neuropathic pain syndromes (Table 11-5) (Bryson, 1996). Selective serotonin reuptake inhibitors do not appear to be as effective as tricyclic antidepressants (Gilron, 2006).

Table 11-5 Antidepressants and Antiepileptic Drugs Used in Chronic Pain Syndromes

Drug (Brand name)	Dosage	Side Effects
Antidepressants		

Tricyclic antidepressants		Dry mouth, constipation, urinary retention, sedation, weight gain
Amitriptyline (Elavil)[a]	For both, 10-25 mg at bedtime; increase by 10-25 mg per week up to 75-150 mg at bedtime or a therapeutic drug level	Tertiary amines have greater anticholinergic side effects
Imipramine (Tofranil)[a]		
Desipramine (Norpramin)[a]	For both, 25 mg in the morning or at bedtime; increase by 25 mg per week up to 150 mg per day or a therapeutic drug level	Secondary amines have fewer anticholinergic side effects
Nortriptyline (Pamelor)[a]		
Selective serotonin reuptake inhibitors		
Fluoxetine (Prozac)[a] Paroxetine (Paxil)[a]	For both, 10-20 mg per day; up to 80 mg per day for fibromyalgia	Nausea, sedation, decreased libido, sexual dysfunction, headache, weight gain
Novel antidepressants		
Bupropion (Wellbutrin)[a]	100 mg per day; increase by 100 mg per week up to 200 mg twice daily (400 mg per day)	Anxiety, insomnia or sedation, weight loss, seizures (at dosages above 450 mg per day)
Venlafaxine (Effexor)[a]	37.5 mg per day; increase by 37.5 mg per week up to 300 mg per day	Headache, nausea, sweating, sedation, hypertension, seizures Serotoninergic properties in dosages below 150 mg per day; mixed serotoninergic and noradrenergic properties in dosages above 150 mg per day
Antiepileptic drugs		
First-generation agents		
Carbamazepine (Tegretol)	200 mg per day; increase by 200 mg per week up to 400 mg three times daily (1200 mg per day)	Dizziness, diplopia, nausea, aplastic anemia
Phenytoin (Dilantin)[a]	100 mg at bedtime; increase weekly up to 500 mg at bedtime	Blood dyscrasias, hepatotoxicity
Second-generation agents		
Gabapentin (Neurontin)	100-300 mg at bedtime; increase by 100 mg every 3 days up to 1800 to 3600 mg per day taken in divided doses three times daily	Drowsiness, dizziness, fatigue, nausea, sedation, weight gain
Pregabalin (Lyrica)	150 mg at bedtime for diabetic neuropathy; 300 mg twice daily for postherpetic neuralgia	Drowsiness, dizziness, fatigue, nausea, sedation, weight gain

Lamotrigine (Lamictal)[a]	50 mg per day; increase by 50 mg every 2 weeks up to 400 mg per day	Dizziness, constipation, nausea; rarely, lifeâ€"threatening rashes

[a] Not approved by the U.S. Food and Drug Administration for treatment of neuropathic pain.

Abbreviated from Maizels, 2005, with permission.

In addition to antidepressants, anticonvulsants have also been used effectively in treatment of CPP. Of these, gabapentin and carbamazepine are most commonly used to reduce neuropathic pain (Wiffen, 2005a, 2005b).

Polypharmacy

Combining drugs with different sites or mechanisms of action may often increase pain relief. For example, an NSAID and an opioid may be partnered, especially in conditions in which inflammation is a dominant component. If muscle spasm underlies pain, then pairing a tranquilizer or a muscle relaxant with an opioid or an NSAID may improve results (Howard, 2003).

SURGERY

Neurolysis

Nerve destruction, termed *neurolysis,* involves nerve transection or injection of a neurotoxic chemical. Nerve transection cuts a specific peripheral nerve or may be performed on an entire nerve plexus.

Presacral neurectomy (PSN) describes interruption of somatic pain fibers from the uterus that course with the primarily sympathetic superior hypogastric plexus. This procedure is performed by incising the pelvic peritoneum over the sacrum and then identifying and transecting the sacral nerve plexus. Alternatively, laparoscopic uterosacral nerve ablation (LUNA) involves the destruction of the uterine nerve fibers that pass to the uterus through the uterosacral ligament. Most surgeons destroy approximately 2 cm of uterosacral ligament near its attachment to the uterus (Lifford, 2002). Based on pelvic innervation, these surgeries are indicated only for treatment of centrally located pelvic pain and have been performed to treat refractory endometriosis-related CPP and dysmenorrhea. In women so treated, approximately 75 percent note a greater than 50 percent decline in pain (American College of Obstetricians and Gynecologists, 2004).

Presacral neurectomy is technically challenging and requires familiarity with operating in the presacral space. Surgery has been associated with long-term constipation and urinary retention postoperatively. Infrequently, life-threatening hemorrhage from the middle sacral vessels may be encountered (Chap. 40, Presacral Venous Plexus).

Hysterectomy

For many women with CPP, especially that is related to organic pathologies, hysterectomy is effective in resolving pain and improving quality of life (Kjerulff, 2000; Stovall, 1990). However, for others, hysterectomy may fail to relieve CPP. This result may follow more commonly in those who are younger than 30 years or those who have depression, psychological problems, or no identifiable pelvic pathology (Gunter, 2003). Almost 40 percent of women with no identified pelvic pathology will have persistent pain post-hysterectomy (Hillis, 1995).

SPECIFIC CAUSES OF CHRONIC PELVIC PAIN

As noted earlier, endometriosis and leiomyomas are common causes of CPP and are discussed in detail in Chapters 9 and 10. Additional potential gynecologic sources of chronic pain include pelvic adhesive disease, ovarian remnant syndrome, and pelvic congestion.

Pelvic Adhesions

Adhesions are fibrous connections between opposing organ surfaces or between an organ and abdominal wall, at sites where there should be no connection. They vary in vascularity and thickness, and commonly are classified according to a system developed by the American Society of Reproductive Medicine (Table 11-6) (American Fertility Society, 1988). These fibrous connections are common, and in laparoscopies performed for CPP, adhesions are found in approximately one quarter of cases (Howard, 1993). However, not all adhesive disease creates pain. For example, Thornton and associates (1997) found no relationship between pelvic

pain and women with intra-abdominal adhesions.

Table 11-6 Adnexal Adhesion Scoring System

Ovary	Adhesions		<1/3 Enclosure	1/3â€“2/3 Enclosure	>2/3 Enclosure
	R	Filmy	1	2	4
		Dense	4	8	16
	L	Filmy	1	2	4
		Dense	4	8	16
Tube	R	Filmy	1	2	4
		Dense	4[a]	8[a]	16
	L	Filmy	1	2	4
		Dense	4[a]	8[a]	16

L = left; R = right.

[a] If the fimbriated end of the fallopian tube is completely enclosed, change the point assignment to 16.

From The American Fertility Society, 1988, with permission.

Pathophysiology

The relationship between chronic pelvic pain and adhesions is incompletely understood. In those with CPP, intraperitoneal adhesions are believed to cause pain when they distort normal anatomy or when activities stretch the peritoneum or organ serosa. This theory is supported by studies using conscious pain mapping, in which filmy adhesions that allowed significant movement between two structures had the highest association with pain, whereas adhesions that prohibited movement had the lowest pain scores. Moreover, adhesions that had a relationship to the peritoneum had a high association with pain (Demco, 2004).

Diagnosis

Risks for adhesions include prior surgery, prior intra-abdominal infection, and endometriosis. Less commonly, inflammation from radiation, chemical irritation, or foreign-body reaction may be contributory. Pain is typically aggravated by sudden movement, intercourse, or other specific activities.

Laparoscopy is the primary tool used to diagnose adhesions. In general, sonography lacks sensitivity, but Guerriero and co-workers (1997) noted a positive correlation with ovarian adhesions if the ovarian surface borders appeared blurred or if the ovary appeared immediately adjacent to the uterus and this position persisted despite transducer manipulation.

Treatment

Surgical lysis is often used to treat pain symptoms, and a number of observational studies have shown pain improvement (Fayez, 1994; Steege 1991; Sutton 1990). However, two randomized studies comparing adhesion lysis with expectant management found no difference in pain scores after 1 year (Peters, 1992; Swank, 2003). In addition, adhesiolysis is associated with a significant risk of adhesiogenesis, especially in cases involving endometriosis (Parker, 2005). Thus, the decision to lyse adhesions should be individualized, and if lysis is performed, steps should be taken to minimize reformation (Hammoud, 2004). Gentle tissue handling, adequate hemostasis, and adhesion barriers have all been shown to be helpful.

Ovarian Remnant Syndrome and Ovarian Retention Syndrome

Following oophorectomy, remnants of an excised ovary may create symptoms that are termed *ovarian remnant syndrome.*

Distinction is made between this syndrome and *ovarian retention syndrome,* also known as *residual ovary syndrome,* which involves symptoms stemming from an ovary intentionally left at the time of previous gynecologic surgery (El Minawi, 1999). Although differentiated by the amount of ovarian tissue involved, both syndromes have nearly identical symptoms and are diagnosed and treated similarly.

Although an uncommon cause of CPP, women with symptomatic ovarian remnants most typically complain of chronic or cyclic pain or dyspareunia. The onset of symptoms is variable and may begin years following surgery (Nezhat, 2005).

Women with these syndromes may have a pelvic mass palpable on bimanual examination (Orford, 1996). Sonography is informative in many cases, and in those with ovarian remnants, ovaries may be identified, in some cases, by a thin rim of ovarian cortex surrounding a co-existent ovarian cyst (Fleischer, 1998). Indeterminate cases may require CT or MR imaging. In cases where ureteral compression is suspected, intravenous pyelography may be warranted. Additionally, laboratory testing, specifically FSH levels in reproductive-aged women with history of a bilateral oophorectomy, may aid diagnosis if these levels fall in premenopausal range (Magtibay, 2005).

Although medical treatment has included hormonal manipulation to suppress functioning tissue, surgical excision is required in most symptomatic cases (Lafferty, 1996). Because the ureter is commonly intimately involved with adhesions encasing a remnant, laparotomy is warranted in most cases. However, in those with advanced laparoscopic skills, successful outcomes have been documented (Nezhat, 2000, 2005).

Pelvic Congestion Syndrome

Retrograde flow through incompetent valves can often create tortuous, congested ovarian or pelvic veins. Chronic pelvic ache, pressure, and heaviness may result and is termed *pelvic congestion syndrome* (PCS) (Beard, 1988).

Pathophysiology

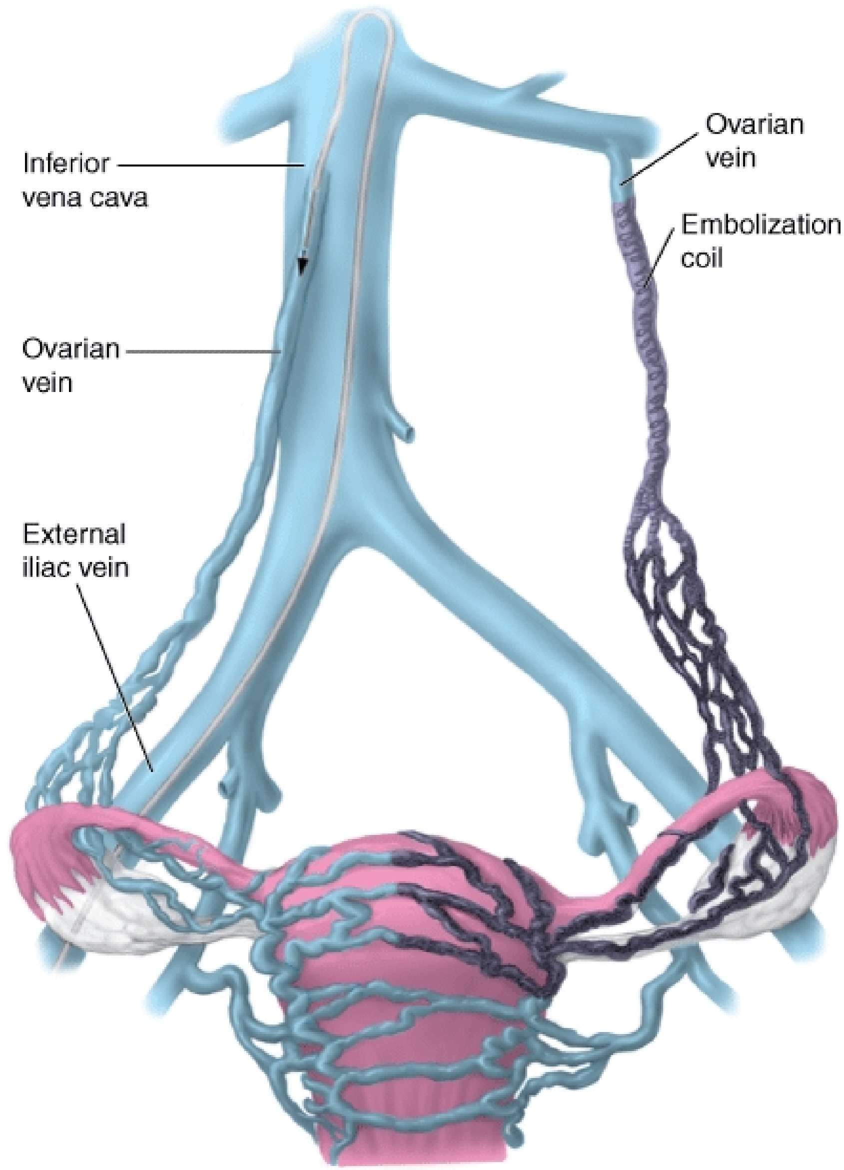
Currently, it is not clear whether congestion results from mechanical dilatation, ovarian hormonal dysfunction, or both. Higher rates of ovarian varicosities and PCS are noted in parous women. A mechanical theory describes a dramatic increase in pelvic vein diameter found in late pregnancy that leads to ovarian vein valve incompetence and pelvic varicosities. Additionally, estrogen has been implicated in PCS in that estrogen acts as a venous dilator. Moreover, PCS resolves following menopause, and anti-estrogenic medical therapy has been shown to be effective in these cases (Farquhar, 1989; Gangar, 1993). Most likely, both factors play roles. The cause of pain with pelvic congestion remains unclear, but increased dilatation, concomitant stasis, and release of local nociceptive mediators have been suggested (Giacchetto, 1989; Soysal, 2001).

Diagnosis

Affected women may describe pelvic ache or heaviness that may worsen premenstrually, after prolonged sitting or standing, or following intercourse. On physical examination, tenderness at the junction of the upper and middle thirds of a line drawn between the symphysis and anterior superior iliac spine or direct ovarian tenderness may be found. In addition, varicosities in the thigh, buttocks, perineum, or vagina may be associated (Venbrux, 1999).

The left ovarian venous plexus drains into the left ovarian vein, which empties into the left renal vein. The right ovarian vein generally drains directly into the inferior vena cava. Both ovarian veins may have numerous trunks (Fig. 11-10). Pelvic venography of this vascular anatomy is a primary diagnostic tool in women suspected of PCS, and embolization can be performed concurrently in identified candidates. Alternatively, CT, MR imaging, sonography, and diagnostic laparoscopy can identify varicosities. However, because these modalities are performed while a woman is prone, some varicosities may decompress and be missed (Park, 2004; Umeoka, 2004).

FIGURE 11-10



On the left, pelvic varices have already been treated with sclerosant and coils in the left ovarian vein. On the right, a guiding catheter is threaded into the right ovarian vein to perform ovarian venography and embolization. *(From Kim, 2006, with permission.)*

Treatment

Treatments for PCS have included chronic progestin or GnRH agonist administration, ovarian vein embolization or ligation, and hysterectomy with bilateral salpingo-oophorectomy (BSO), although none is definitive. For example, Beard and colleagues (1991) found that almost one third of women had some residual pain following total hysterectomy with BSO for this condition.

Embolization appears to afford effective treatment, and percentages of women with pain improvement range from 65 to 95 percent (Kim, 2006; Maleux, 2000; Venbrux, 2002). Chung and co-workers (2003) compared embolization against hysterectomy and oophorectomy and found embolization more effective. Long-term studies on its effects past 1 year, however, are lacking.

Alternatively, medical treatment with GnRH agonists (see Table 9-3) or medroxyprogesterone acetate, 30 mg orally daily, has been shown to be effective for some women with PCS, although symptoms typically recur after medication is discontinued (Reginald, 1989).

Dysmenorrhea

Cyclic pain with menstruation is common and accompanies most menses (Balbi, 2000; Weissman, 2004). This pain is classically described as cramping and is often accompanied by low backache, nausea and vomiting, headache, or diarrhea.

The term, *primary dysmenorrhea* , describes cyclic menstrual pain without an identifiable associated pathology, whereas *secondary dysmenorrhea* frequently complicates endometriosis, leiomyomas, PID, adenomyosis, endometrial polyps, and menstrual outlet obstruction. For this reason, secondary dysmenorrhea may be associated with other gynecologic symptoms, such as dyspareunia, dysuria, abnormal bleeding, or infertility.

Compared with secondary dysmenorrhea, primary dysmenorrhea more commonly begins shortly after menarche. Pain characteristics, however, typically fail to differentiate between the two types, and primary dysmenorrhea is usually diagnosed following exclusion of known associated causes.

RISKS FOR PRIMARY DYSMENORRHEA

When other factors are removed, primary dysmenorrhea equally affects women regardless of age, race, and socioeconomic status. However, increased pain duration or severity is positively associated with earlier age at menarche, long menstrual periods, smoking, and increased body mass index (BMI). In contrast, parity appears to improve symptoms (Harlow, 1996; Sundell, 1990).

PATHOPHYSIOLOGY

During endometrial sloughing, endometrial cells release prostaglandins as menstruation begins. Prostaglandins stimulate myometrial contractions and ischemia. Women with more severe dysmenorrhea have higher levels of prostaglandins in menstrual fluid, and these levels are highest during the first 2 days of menstruation. Prostaglandins are also implicated in secondary dysmenorrhea, however, anatomic mechanisms can also be identified, depending on the type of accompanying pelvic disease.

DIAGNOSIS

In women with menstrual cramps and no other associated findings or symptoms, no additional evaluation may be initially required, and empiric therapy may be prescribed (Proctor, 2006). In women at risk for PID, cultures for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are indicated. Moreover, if pelvic evaluation is incomplete due to body habitus, then transvaginal sonography may be informative to exclude structural pelvic pathology.

TREATMENT

Nonsteroidal Anti-Inflammatory Drugs

Because prostaglandins have been implicated in the genesis of dysmenorrhea, administration of NSAIDs is logical, and studies support their use (Marjoribanks, 2003; Zhang, 1998). These drugs and their dosages are found in Table 10-2.

Steroid Hormone Contraception

Combination hormone birth control methods are believed to improve dysmenorrhea by lowering prostaglandin production and observation studies of combination oral contraceptives (COCs) have noted improved dysmenorrhea in users (Brill, 1991; Gauthier, 1992; Hendrix, 2002; Milsom, 1990). In addition, extended or continuous administration of COCs may be useful in women with pain not controlled with traditional pill use (see Chap. 5, Estrogen Plus Progestin Contraceptives) (Sulak, 1997).

Progestin only contraceptives are also used to effectively treat dysmenorrhea. The levonorgestrel-releasing intrauterine system (LNG-IUS), depot medroxyprogesterone acetate injection, and progestin-releasing implanted rods have been shown to be effective in improving dysmenorrhea (see Chap. 5, Injectable Progestin Contraceptives) (Baldaszti, 2003; Varma, 2006).

Gonadotropin-Releasing Hormone Agonists and Androgens

The estrogen-lowering effects of these agents lead to endometrial atrophy and diminished prostaglandin production. Although

gonadotropin-releasing hormone agonists and androgens such as danazol have been shown to be effective in treating dysmenorrhea, their substantial side effects preclude their routine and long-term use. A fuller discussion and list of dosages for these agents and their side effects can be found in Chapter 9, GnRH Agonists.

Complementary and Alternative Medicine

Diet changes, herbal medicine, and physical treatments have each been sparsely evaluated in the treatment of dysmenorrhea. Oral vitamins E and B_1 (thiamine), magnesium, fish oil, low-fat diet, and the herb Toki-shakuyaku-san (TSS), have all been shown to improve dysmenorrhea, but evidence derives from small and typically nonrandomized trials (Barnard, 2000; Gokhale, 1996; Harel, 1996; Wilson, 2001; Ziaei, 2001). Additionally, data are limited but positive toward the use of exercise, topical heat, acupuncture, and transcutaneous electrical nerve stimulation (TENS) (Akin, 2001, 2004; Fugh-Berman, 2003; Golub, 1968; Helms, 1987; Kaplan, 1994).

Surgery

Cases of dysmenorrhea refractory to conservative management are unusual, and in such instances, surgery may be warranted. Hysterectomy is effective in treating dysmenorrhea, but may be unwanted in those desiring future fertility. For these women, LUNA or presacral neurectomy may be indicated (Neurolysis). There is limited evidence to support the use of surgery for primary dysmenorrhea, but comparisons of LUNA and presacral neurectomy show significantly greater long-term pain relief with presacral neurectomy (Proctor, 2005).

Dyspareunia

Dyspareunia is a frequent gynecologic complaint and in reproductive-aged U.S. women, the 12-month prevalence is noted to be 15 to 20 percent (Glatt, 1990; Laumann, 1999). Painful intercourse may be associated with vulvar, visceral, musculoskeletal, neurogenic, or psychosomatic disorders. Moreover, co-existent etiologies may lead to similar symptoms. For example, women with vulvodynia have been shown in many cases to have co-existent pelvic floor muscle spasm, both of which may cause dyspareunia (Reissing, 2005). Because of the frequent association between dyspareunia and CPP and frequent overlap of etiologies, physical examination and diagnostic testing often follow that for women with CPP (Physical Examination).

Dyspareunia may be subclassified as *insertional,* that is, pain with vaginal entry, or *deep* , which is associated with deep thrusting. Vulvodynia, vulvitis, and poor lubrication comprise the bulk of insertional dyspareunia, whereas endometriosis, pelvic adhesions, and bulky leiomyomas are frequent causes of deep dyspareunia. However, in many women, both insertional and thrust dyspareunia may be present.

Additional terms include *primary dyspareunia* and *secondary dyspareunia,* which describe the onset of pain coincident with coitarche or after a period of pain-free intercourse, respectively. Although sexual abuse, female genital mutilation, and congenital anomalies most frequently lead to primary dyspareunia, sources of secondary dyspareunia are more varied. Lastly, dyspareunia should be clarified as *generalized,* occurring in all episodes of intercourse or as *situational,* associated with only specific partners or sexual positions.

DIAGNOSIS

History taking in women with dyspareunia should include questions about associated symptoms such as vaginal discharge, vulvar pain, dysmenorrhea, CPP, or scant lubrication. Onset of symptoms and other associated events such as obstetric delivery, pelvic surgery, or sexual abuse is often informative. In addition, dyspareunia may be found in those who breast feed, presumably because of hypoestrogenism seen with lactation (Buhling, 2006; Signorello, 2001). Psychosocial topics such as relationship satisfaction or depression should also be covered.

Inspection of the vulva should follow that for chronic pain. In particular, generalized erythema, episiotomy scars, or atrophy is sought. Erythema may indicate contact or allergic dermatitis or infection, particularly fungal infection (Chap. 4). Accordingly, a historical inventory of potential skin irritants, a saline slide preparation, vaginal pH testing, and vaginal cultures are performed. Specifically, a vaginal fungal culture may be required in some cases because several noncandidal species may be difficult to detect with only microscopic analysis (Edwards, 2003; Haefner, 2005).

Some, but not all, have found a positive correlation between degree of pelvic organ prolapse and dyspareunia (Burrows, 2004; Ellerkmann, 2001). If noted, its degree should be assessed with pelvic organ prolapse evaluation (POP-Q) (see Chap. 24, Pelvic Organ Prolapse Quantification (POP-Q)).

Physical examination may begin with palpation of the Bartholin and periurethral glands. Additionally, cotton swab testing is used to map painful areas (see Fig. 4-11). Insertion of a single digit into the vagina may elicit *vaginismus,* that is, reflex contraction of the muscles associated with distal vaginal penetration (Basson, 2000). Spasm is thought to be a conditioned response to a current or former physical pain, and the bulbocavernosus, pubococcygeus, piriformis, and obturator internus muscles are most typically involved (Bachmann, 1998).

With deeper insertion, digital examination may trigger midvaginal pain, which may be seen with interstitial cystitis, congenital anomalies, or following radiation therapy or pelvic reconstructive surgeries.

Etiologies of deep dyspareunia more commonly mirror those for CPP and focal points of examination are discussed on page 253. Similarly, diagnostic testing in great part mirrors that for CPP. Urine and vaginal cultures may indicate infection, and radiologic imaging may reveal structural visceral disease.

TREATMENT

Resolution of dyspareunia is highly dependent on the underlying cause. For those with vaginismus, structured desensitization is effective. Patients gradually gain control in comfortably inserting dilators of increasing size into the introitus. Concurrent psychological counseling in such cases is often warranted. Poor lubrication may be countered with education directed toward adequate arousal techniques and use of external lubricants.

Surgery may be indicated for structural pathologies and may include ablation of endometriosis, lysis of adhesions, and restoration of normal anatomy in cases of congenital anomalies or female genital mutilation (Nour, 2006). For those with dyspareunia related to a retroverted uterine position, uterine suspension has been shown, although in small studies, to be effective (Perry, 2005).

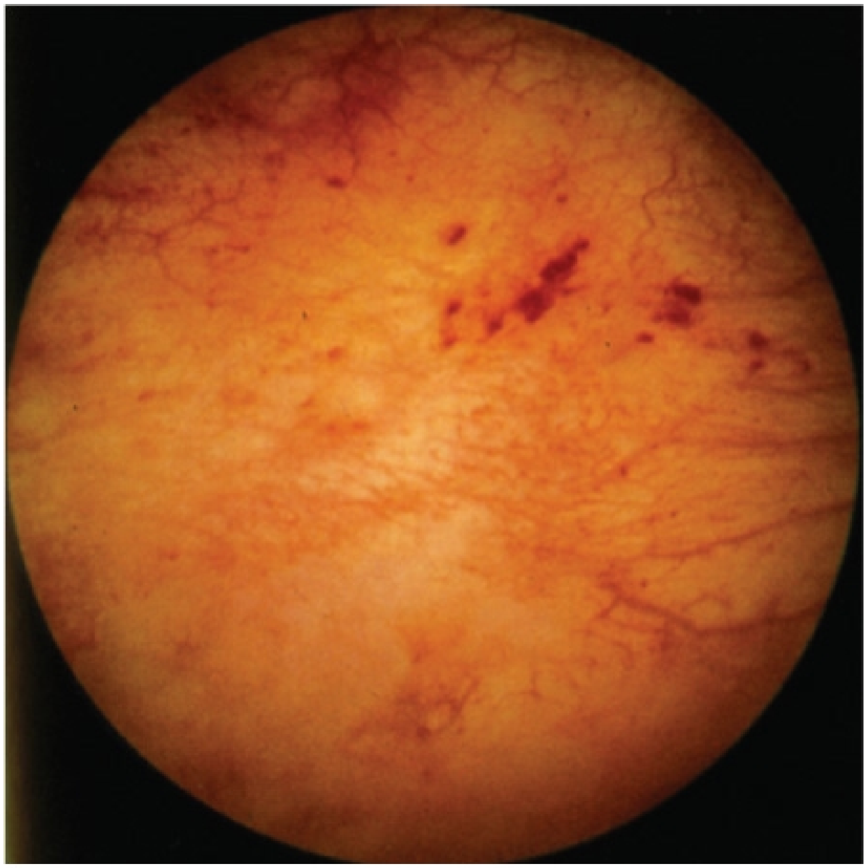
Dysuria

Evaluation of dysuria begins with a careful pelvic inspection to exclude vaginitis, vulvar lesions, and urethral diverticulum. A voiding diary can be informative, and for those with associated dyspareunia, a sexual inventory should be obtained. The most common cause of dysuria is infection, and urinalysis and urine culture are therefore initial tests (see Chap. 3, Diagnosis). Similarly, *Chlamydia trachomatis* and herpes simplex virus infections should be excluded. For those with chronic dysuria, urodynamic studies may help to identify those with detrusor overactivity, significantly decreased compliance, or bladder outlet obstruction (see Chap. 23, Diagnostic Testing). Cystoscopy is used to identify the hallmark mucosal findings of interstitial cystitis and exclude neoplastic growths or stones (Irwin, 2005). Adjunctively, sonography or laparoscopy may be indicated to exclude structural pelvic pathology or endometriosis.

INTERSTITIAL CYSTITIS

This chronic inflammatory disorder of the bladder is typified by symptoms of frequency, urgency, and pelvic pain (Bogart, 2007). With interstitial cystitis (IC), this triad is found in combination with characteristic mucosal changes and reduced bladder capacity (Hanno, 1994). Cystoscopically, *Hunner ulcers* are reddish-brown mucosal lesions with small vessels radiating toward a central scar and are found in approximately 10 percent of cases (Fig. 11-11) (Messing, 1978; Nigro, 1997). The other more common finding is *glomerulations,* which are small petechiae or submucosal hemorrhages.

FIGURE 11-11



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Cystoscopic photograph displays Hunner ulcers. *(From Reuter, 1987, with permission.)*

In addition to women with classic IC findings, the International Continence Society (ICS) has created an additional category to describe those with chronic IC symptoms, but who lack cystoscopic findings. *Painful bladder syndrome* describes symptoms of IC but in the absence of proven urinary infection or other obvious pathology (Abrams, 2002).

Prevalence

The prevalence of IC in the United States is variable and cited at 30 to 60 per 100,000 (Curhan, 1999; Jones, 1997). It is diagnosed more commonly in women, in Caucasians, in smokers, and in those in their 40s (Kennedy, 2006; Propert, 2000). In addition, IC is seen in association with irritable bowel syndrome, generalized pain disorders, fibromyalgia, pelvic floor dysfunction, and depression (Aaron, 2000; Clauw, 1997; Novi, 2005; Peters, 2007).

Pathophysiology

The exact cause of IC is not known, and current theories include increased mucosal permeability or mast cell activation (Sant, 2007; Warren, 2002). Glycosaminoglycans are an important component of the mucin layer that covers and protects the bladder urothelium. One theory explains that IC symptoms originate from an increased bladder mucosa permeability that results from a defect in the protective bladder glycosaminoglycan component (Parsons, 2003).

Diagnosis

Koziol (1994) reported symptoms in a series of IC sufferers and found frequency, urgency, and pelvic pain to be most common.

Frequency occurs both in the day and night, and voiding events average 16 times per day but can reach 40 times daily. Pain is described as vaginal, suprapubic, or lower abdominal and often worsens during the week before menstruation. It is commonly exacerbated by spicy foods; alcoholic, acidic, carbonated, and caffeinated beverages; and by coitus, stress, and exercise. Pain is often relieved with voiding small amounts of urine, but typically recurs as the bladder refills. Additionally, women commonly describe dyspareunia (Metts, 2001).

Many other conditions can produce similar symptoms to IC, and most urologists have therefore regarded IC as being a diagnosis of exclusion. Accordingly, patients suspected of having IC typically undergo cystoscopy. Bladder biopsy is not required to diagnose IC, but biopsies are often performed to exclude other bladder pathology such as cancer. Urodynamic testing is recommended in those with urgency. In women with IC, both bladder capacity and compliance are decreased.

Treatment

Interstitial cystitis is a chronic disorder with exacerbations and remissions. There is no universally accepted therapy, and for some, expectant management is appropriate. Of therapies, hydrodistention, amitriptyline, bladder analgesics, dietary restriction, and intravesical heparin or pentosanpolysulfate are among the more commonly used (Rovner, 2000). The Interstitial Cystitis Association serves as an important resource to patients and clinicians for therapy options and other needs (http://www.ichelp.org).

GASTROINTESTINAL DISEASE

In a significant number of cases, gastrointestinal disease is found as an underlying cause of chronic pelvic pain. Zondervan and associates (1999) followed a cohort of women with CPP and found that irritable bowel syndrome and interstitial cystitis were the most common diagnoses. As seen in Table 11-1, GI causes may be organic or functional. Symptoms such as fever, gastrointestinal bleeding, weight loss, anemia, and abdominal mass should prompt evaluation for organic pathology. Initial screening may follow that for CPP, but for those with diarrheal states, additional stool examination for leukocytes or ova and parasites may be indicated. Investigations may include a sigmoidoscopy or colonoscopy to exclude inflammation or tumors. When indicated, sonography may aid in distinguishing gastrointestinal from gynecologic pathology.

Functional Bowel Disorders

Also known as *functional gastrointestinal disorders* (FGIDs), this group of functional disorders has symptoms attributable to the lower GI tract and includes those listed in Table 11-7. In defining these chronic conditions, symptoms must have begun more than 6 months previously and have occurred more than 3 days a month during the last 3 months (Longstreth, 2006). The diagnosis always presumes the absence of a structural or biochemical explanation for symptoms (Thompson, 1999).

Table 11-7 Functional Gastrointestinal (GI) Disorders

Functional bowel disorders	
Irritable bowel syndrome (IBS)	Recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months associated with 2 or more of the following: (1) improved with defecation; (2) onset associated with a change in stooling frequency; (3) onset associated with a change in form of stool
Functional abdominal bloating	Must include *both* of the following: (1) recurrent feeling of bloating or visible distention at least 3 days/month in 3 months; (2) insufficient criteria for a diagnosis of functional dyspepsia, IBS, or other functional GI disorder
Functional constipation	Must include *two or more* of the following: (1) straining during at least 25% of defecations; (2) lumpy or hard stools in at least 25% of defecations; (3) sensation of incomplete evacuation for at least 25% of defecations; (4) sensation of anorectal obstruction/blockage for at least 25% of defecations; (5) manual maneuvers to aid at least 25% of defecations; (6) fewer than three defecations per week Loose stools are rarely present without the use of laxatives There are insufficient criteria for IBS
Functional diarrhea	Loose or watery stools without pain, occurring in at least 75% of stools
Unspecified functional bowel disorder	Bowel symptoms not attributable to an organic etiology that do not meet criteria for the previously defined categories
Functional abdominal pain	
Functional abdominal pain	At least 6 months of: (1) continuous or nearly continuous abdominal pain; and (2) no or only occasional relation of pain with physiologic events (e.g., eating, defecation, or menses); (3) some loss of daily functioning; (4) pain is not feigned (e.g., malingering); (5) insufficient criteria for other functional gastrointestinal disorders that would explain the abdominal pain
Unspecified functional abdominal pain	

Adapted from Longstreth, 2006, and Thompson, 1999, with permission.

IRRITABLE BOWEL SYNDROME

Definition and Incidence

This functional bowel disorder is defined as abdominal pain or discomfort with defecation or with a change in bowel habits. Subtypes are divided by the predominant stool pattern and include constipative, diarrheal, and mixed stool categories. Although defining criteria are listed in Table 11-7, other symptoms that may support the diagnosis include abnormal stool frequency (fewer than three bowel movements per week or more than three per day), abnormal stool form, straining, urgency, passing mucus, and bloating (Longstreth, 2006).

Irritable bowel syndrome (IBS) is common, and its prevalence in the general population is estimated to be near 10 percent. The prevalences of diarrhea-predominant and constipation-predominant IBS are equivalent and both are approximately 5 percent (Saito, 2002).

Pathophysiology

With IBS, neural, hormonal, genetic, environmental, and psychosocial factors are variably involved (Drossman, 2002). The primary pathophysiologic mechanism of IBS, however, is thought to involve dysregulation in interactions between the central nervous system (CNS) and enteric nervous system (ENS). Such brain-gut dysfunction may eventually cause alterations of gastrointestinal mucosal immune response, intestinal motility and permeability, and visceral sensitivity. These in turn produce abdominal pain and altered bowel function (Harris, 2006). Specifically, serotonin (5-hydroxytryptamine, 5-HT) is involved with regulating intestinal motility, visceral sensitivity, and gut secretion and is thought to play an important role in IBS (Atkinson, 2006; Gershon, 2005).

Diagnosis

Organic diseases such as those in Table 11-1 are excluded prior to the diagnosis of IBS, although for patients who have typical IBS symptoms and no symptoms of organic disease, few tests are required. Testing is based on a patient's age, duration and severity of symptoms, psychosocial factors, presence of organic disease symptoms, and family history of gastrointestinal disease.

TREATMENT

Diet

Traditionally, therapy to increase daily fiber intake has been used. Although dietary fiber is effective in treating constipation, it has not been shown to be effective for diarrhea-dominant cases of IBS or for IBS-associated pain (Quartero, 2005). Management of food intolerances can be another potentially valuable treatment adjunct (Alpers, 2006).

Medications

In general, drug therapy is directed toward dominant symptoms (Fig. 11-12). For those with constipation-dominant IBS, commercial fiber analogs may help if increased dietary fiber is unsuccessful (Table 11-8) (Ramkumar, 2005). In addition, stimulation of the serotonin receptor subtype 5-hydroxytryptamine-4 (5-HT$_4$) increases colonic transit time and inhibits visceral sensitivity. Specifically, tegaserod (Zelnorm, Novartis, East Hanover, NJ), a partial 5-HT$_4$ receptor agonist, increases colonic motility and has been effective in relief of constipation-predominant IBS (Layer, 2005; Tack, 2005). However, in 2007, Novartis suspended U.S. sales of Zelnorm in compliance with a request by the Food and Drug Administration (FDA). An increased incidence of cardiovascular events in those using this agent prompt the FDA's action.

Table 11-8 Agents Used to Treat Irritable Bowel Syndrome (IBS)

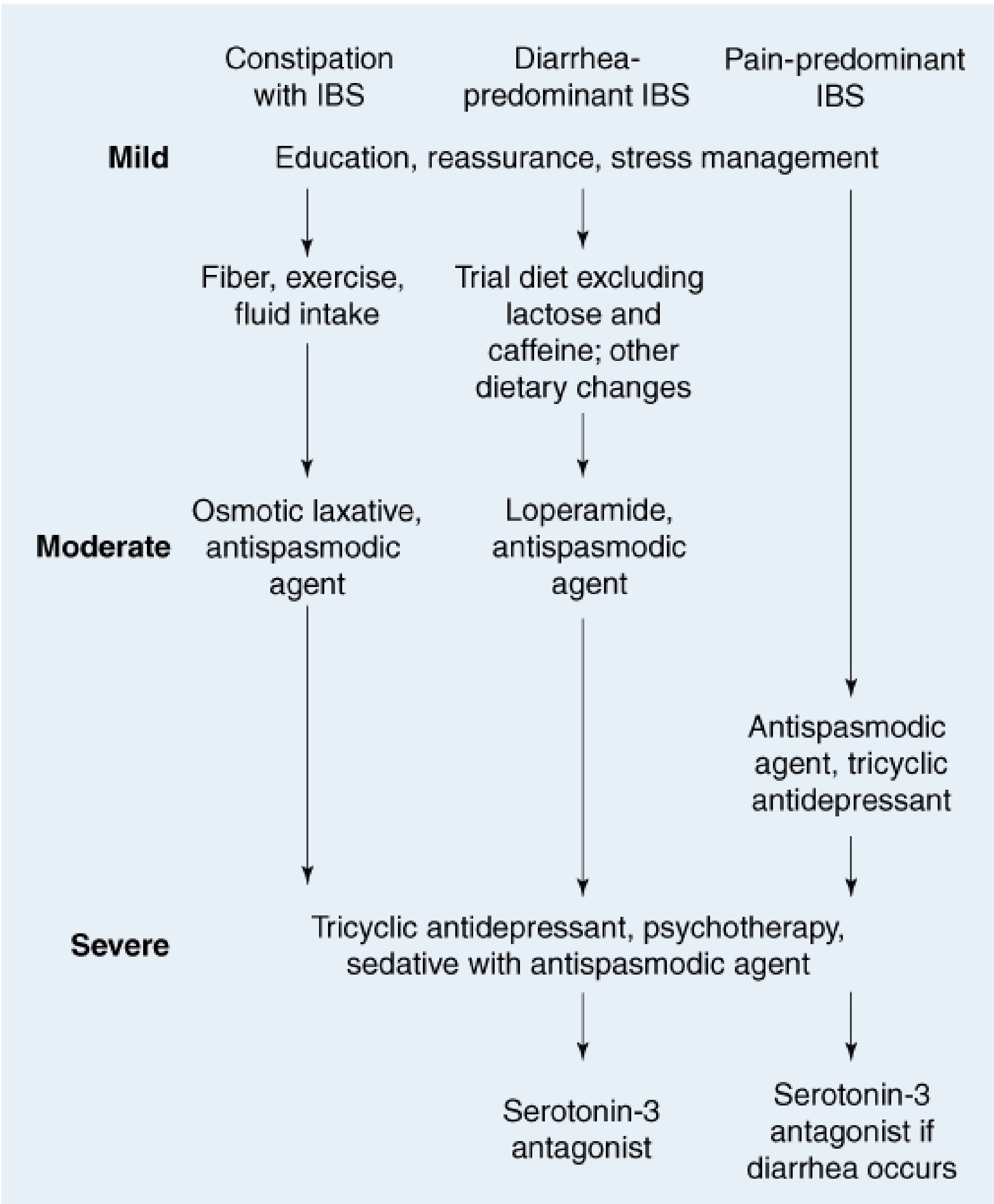
Symptom	Drug	Oral Dosage
Diarrhea	Loperamide	2â€“4 mg when necessary; maximum 12 g/d
	Cholestyramine resin	4 g with meals
	Alosetron	0.5â€“1 mg bid (for severe IBS)
Constipation	Psyllium husk	3.4 g bid with meals, then adjust
	Methylcellulose	2 g bid with meals, then adjust
	Calcium polycarbophil	1 g qd to qid
	Lactulose syrup	10â€“20 g bid
	70% sorbitol	15 mL bid
	Polyethylene glycol 3350	17 g in 8 oz. water qd
	Magnesium hydroxide	2â€“4 tbsp qd
Abdominal pain	Tricyclic antidepressants	Start at 25â€“50 mg hs, then adjust

	Selective serotonin reuptake inhibitors	Begin with a small dose and increase as needed

bid = twice daily; hs = at bedtime; qd = daily, qid = four times daily.

Modified from Longstreth, 2006, with permission.

FIGURE 11-12



Algorithm for the treatment of irritable bowel syndrome. *(Modified from Mertz, 2003, with permission.)*

For those with diarrhea-dominant symptoms, loperamide (Imodium, McNeil PPC, Fort Washington, PA) or diphenoxylate (Lomotil, Pfizer, New York, NY) are effective in slowing bowel motility. As substances stay longer in the intestine, more water is absorbed from fecal matter. Thus, for those with severe diarrhea, alosetron (Lotronex, GlaxoSmithKline, Philadelphia, PA), a selective serotonin 5-HT_3 receptor antagonist, interacts with receptors of enteric nervous system neurons to decrease pain, urgency, and stool frequency (Camilleri, 2000; Chey, 2004).

For patients with pain, antispasmodic agents decrease intestinal smooth muscle activity and are thought to decrease abdominal discomfort if pain is secondary to spasm. Agents available in the U.S. include dicyclomine (Bentyl) and hyoscyamine (Levsin). In general, these agents are safe, inexpensive, and have been shown to be effective (Quartero, 2005). However, evidence-based data supporting their use are small, and anticholinergic side effects of these agents often limit their long-term use (Schoenfeld, 2005).

Tricyclic antidepressants may help patients with IBS both by an anticholinergic effect on the gut and mood-modifying action. Tricyclic antidepressants may slow intestinal transit time and have been shown to be effective in treatment of diarrhea-dominant IBS (Hadley, 2005). Alternatively, another class of antidepressant, the selective serotonin reuptake inhibitors (SSRIs), has been shown in small studies to be useful for irritable bowel syndrome (Tabas, 2004; Vahedi, 2005).

Psychological Therapy

Psychological or behavioral treatments may help some patients. Of these, cognitive-behavioral therapy and hypnotherapy have been shown to be effective (Drossman, 2003; Gonsalkorale, 2003; Payne, 1995).

MUSCULOSKELETAL

In the search for visceral sources of pelvic pain, the evaluation for musculoskeletal disorders is sometimes minimized by gynecologists. Yet potential causes are numerous.

Myofascial Pain Syndrome

A hyperirritable area within a muscle can lead to persistently contracted fibers and cause pain, weakness, or autonomic reactions (Simons, 1999). The primary reactive area within the muscle is termed a *trigger point* (TrP) and is identified as a palpable taut, ropy band. Myofascial trigger points can affect any muscle, and those involving muscles of the anterior abdominal wall, pelvic floor, and pelvic girdle can be sources of chronic pelvic pain. For this reason, the American College of Obstetricians and Gynecologists (1988) recommends an assessment of the musculoskeletal system prior to laparoscopy or hysterectomy for CPP.

PATHOPHYSIOLOGY

Trigger points are thought to form as the end of a metabolic crisis within a muscle. Dysfunction of a neuromuscular endplate can lead to sustained acetylcholine release, persistent depolarization and sarcomere shortening, and creation of a taut muscle band. Affected fibers compress capillaries and decrease local blood flow. The resulting ischemia leads to release of substances that activate peripheral nerve nociceptors, and in turn cause pain (McPartland, 2004).

A persistent barrage of nociceptive signals from TrPs may eventually lead to central sensitization and the potential for neuropathic pain (Neuropathic Pain). Signals may spread segmentally within the spinal cord to cause localized or referred pain (Gerwin, 2005). Trigger points can also initiate somatovisceral responses such as vomiting, diarrhea, and bladder spasm, which may add confusion to the diagnosis.

INCIDENCE AND RISK FACTORS

The incidence of myofascial disease is unknown, but in an evaluation of 500 patients with chronic pelvic pain, Carter (1998) found 7 percent of patients primarily had trigger points as a source of their pain. Prevalence appears to be greatest in those between 30 and 50 years of age. Risk factors are varied, although many trigger points can be traced to a prior specific trauma such as a sporting injury or to chronic biomechanical overload of a muscle (Sharp, 2003). Accordingly, in evaluating patients with chronic pain and suspected myofascial pain syndrome (MPS), a detailed inventory of sporting injuries, traumatic injuries, surgeries, and work activities is essential.

DIAGNOSIS

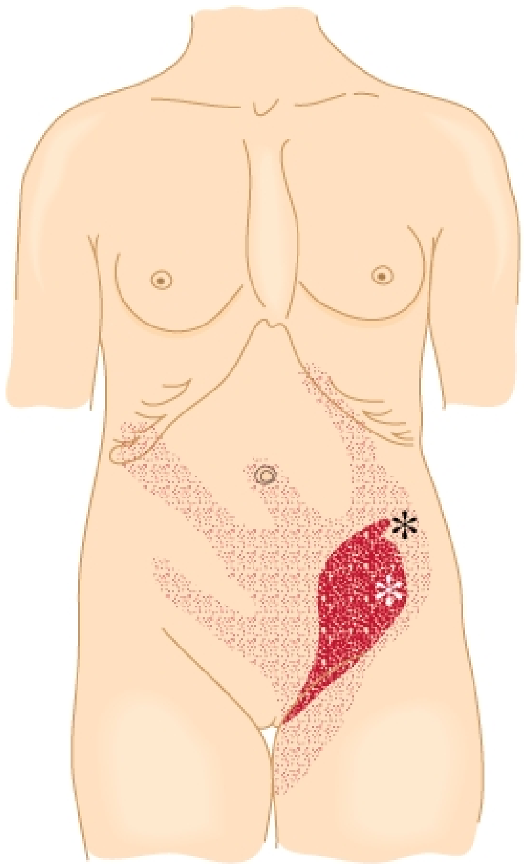
Patients typically describe the pain as aggravated by specific movement or activity and relieved by certain positions. Pressure on a TrP and cold, damp exposure generally worsens pain.

During examination, flat palpation, pincer palpation, and deep palpation may each be required, depending on muscle location, to locate a Trp. Flat palpation uses fingertips to roll over superficial muscles that have only one surface available. In those muscles with greater accessibility, pincer palpation grasps the muscle belly between the thumb and fingers. Finally, digital probing is required for deep muscles. In those with MPS, spot tenderness and taut muscle bands are appreciated. Classically, the involved muscle displays weakness and restricted stretch. Additionally, TrP pressure may also elicit a local muscle twitch response or reproduce a patient's referred pain or both.

MUSCLE GROUPS

Identification by the patient of painful sites on a pain diagram can be an informative first step (see Fig. 11-5). Involvement of specific muscles will often give characteristic patterns (Fig. 11-13).

FIGURE 11-13



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Drawing illustrates that anterior abdominal wall muscle trigger points can create extensive patterns of referred pain. Asterisks are trigger points. Dark and light stippling reflect varying patterns of referred pain. *(From Costello, 1998, with permission.)*

Abdominal Wall Muscles

Rectus abdominis, the obliques, and transversus abdominis muscles may all develop TrPs that lead to CPP. Associated somatovisceral pelvic symptoms from these muscles may include diarrhea or urinary frequency, urgency, or retention.

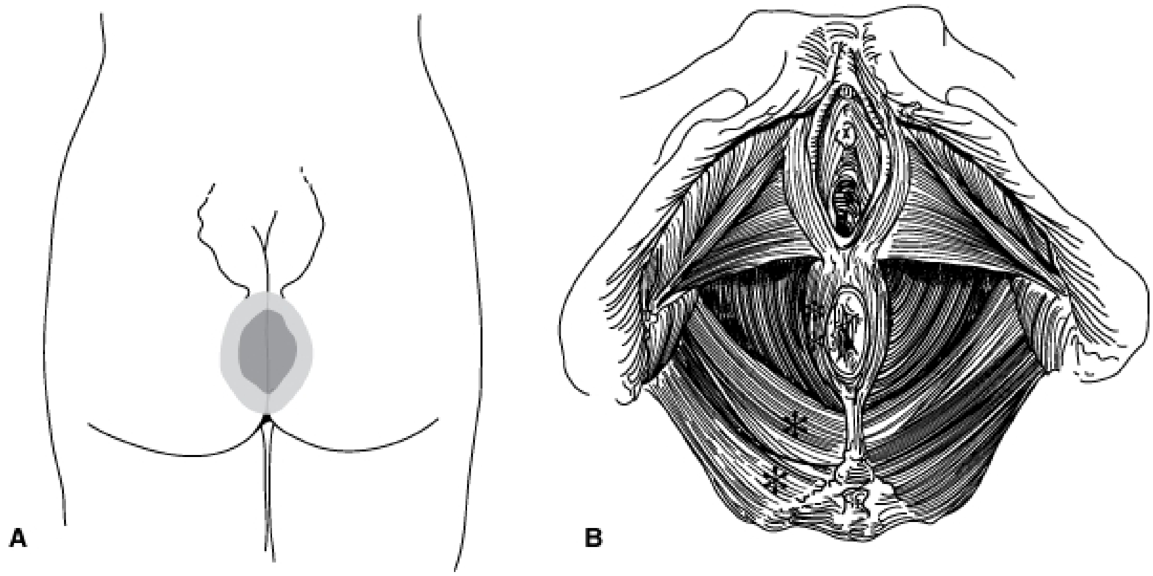
Painful TrPs are frequently found along the lateral margin of the rectus abdominis muscles, termed the linea semilunaris (Suleiman,

2001). Additionally, TrPs in the rectus abdominis muscle commonly develop below the umbilicus and at the muscle's insertion into the pubic bone. Trigger points of the external oblique frequently involve its lateral attachment to the anterior iliac crest and pain usually refers to the pubic bone.

Pelvic Floor Muscles

Trigger points involving the levator ani, coccygeus, and anal sphincter muscles are frequently associated with poorly localized pain that may be described as involving the coccyx, hip, or back (Fig. 11-14). Dyspareunia is common. Palpation of these muscles for TrPs mirrors that described earlier in the examination for chronic pelvic pain (Abdominal Examination).

FIGURE 11-14



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Myofascial trigger points **A.** Drawing illustrating some of the different referred pain patterns (dark and light shading). **B.** Trigger points are seen (asterisks) points in the external anal sphincter, levator ani, and coccygeus muscles. *(From Costello, 1998, with permission.)*

Pain stemming from TrPs involving the levator ani muscles has had a variety of names including *levator ani spasm syndrome* and *coccydynia.* Currently, *levator ani syndrome* is the preferred term and coccydynia is reserved for coccygeal pain originating from skeletal trauma to the coccyx.

Perineal Muscles

The superficial transverse perineal, bulbocavernosus, and ischiocavernosus muscles can be assessed with flat palpation for TrPs.

Pelvic Wall Muscles

Trigger points involving the obturator internus muscle may lead to vaginal, anal, coccygeal, or posterior thigh pain. With the patient supine and hip straight, medial rotation may be limited.

Additionally, patients may have involvement of muscles that support the pelvic bones. In general, TrPs within the gluteus muscles, piriformis, and iliopsoas will have additional referred pain to the groin or buttock or both.

TREATMENT

The goal of treatment is inactivation of trigger points, which then allows stretching and release of taut muscle bands. Therapies are varied and include, among others: TrP release maneuvers, biofeedback, TrP dry needling or injection, local heat, and pharmacologic agents such as NSAIDs, other analgesics, muscle relaxants, and tranquilizers.

NEUROLOGIC

Nerve Entrapment

Anterior abdominal wall pain is frequently mistaken for visceral pain, and common causes include nerve entrapment of the anterior cutaneous branches of the intercostal, ilioinguinal, iliohypogastric, genitofemoral nerves, and lateral femoral cutaneous nerve branches (Greenbaum, 1994).

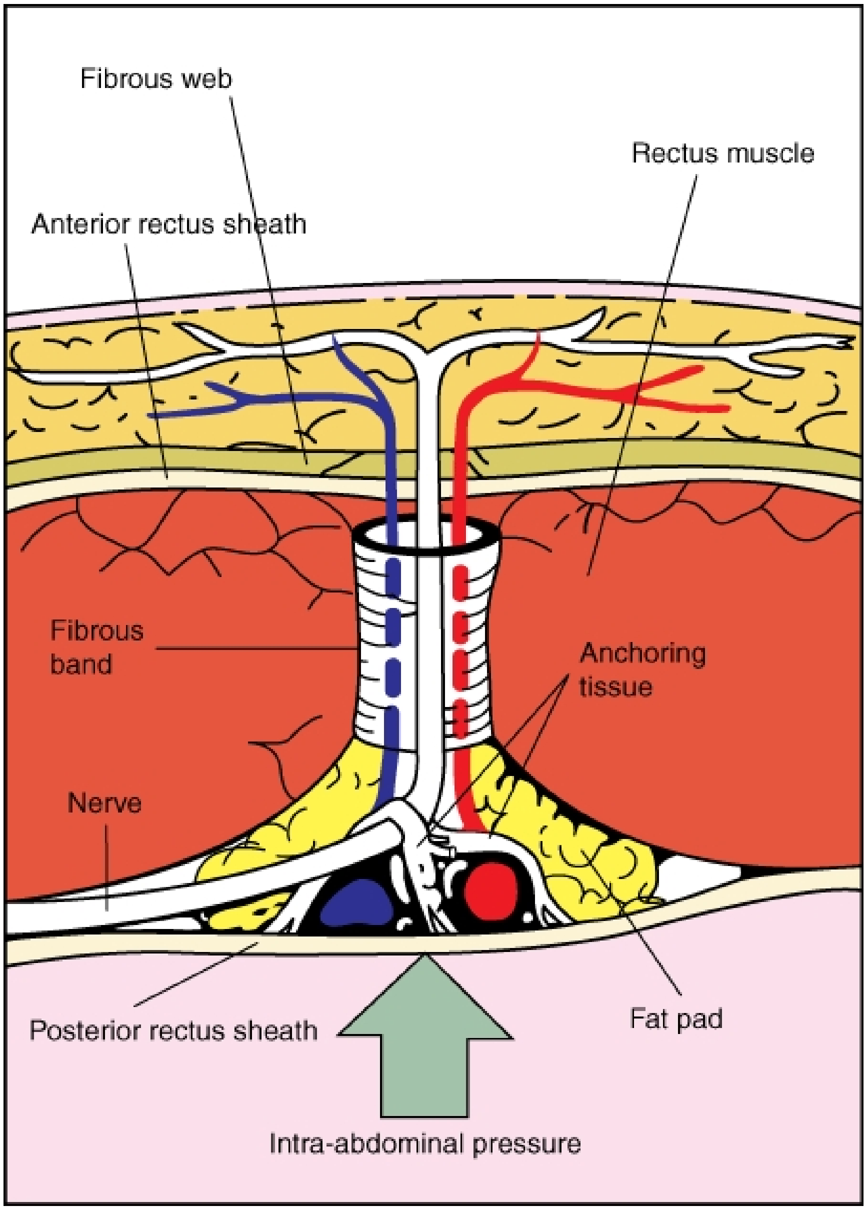
Alternatively, exertion-related swelling of the piriformis muscle, termed *piriformis syndrome,* may lead to buttock and posterior leg pain in the distribution of the sciatic nerve (Broadhurst, 2007; Fishman, 2002). Nerve entrapment neuropathies of the pudendal nerve may lead to perineal pain or fecal incontinence (Gooneratne, 2007).

PATHOPHYSIOLOGY

Peripheral nerves may be compressed either within narrow anatomic canals or rings, or beneath tight ligaments, fibrous bands, or sutures. Thus, common sites of compression for a given nerve are often predictable based on their anatomy.

Each anterior cutaneous branch of the intercostal nerves traverses anteriorly through the rectus abdominis muscle. Each branch and its corresponding vessels travels through a fibrous ring found within the lateral aspect of rectus abdominis muscle and medial to the linea semilunaris (Fig. 11-15). On crossing the anterior rectus sheath, each branch divides and then courses within the subcutaneous tissues. Fat surrounding the neurovascular bundle appears to pad the enclosed structures within the fibrous ring (Srinivasan, 2002). However, if this bundle receives excessive intra- or extra-abdominal pressure, compression of the bundle against the fibrous ring causes nerve ischemia and pain (Applegate, 1997).

FIGURE 11-15



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Drawing displays anterior abdominal cutaneous nerve entrapment. *(Redrawn from Greenbaum, 1994, with permission.)*

Alternatively, nerve entrapment, injury, or neuroma formation involving branches of the ilioinguinal, iliohypogastric, lateral femoral cutaneous nerve or genitofemoral nerves may follow inguinal hernia repair, low transverse abdominal incisions such as a Pfannenstiel incision, and lower abdominal incisions for laparoscopic trocar placement (see Section 41-2, Pfannenstiel Incision and Section 41-28, Laparoscopy). Hypoesthesia is the more common finding with these injuries, but pain may variably develop within months of surgery or after several years.

DIAGNOSIS AND TREATMENT

Criteria for diagnosing nerve entrapment are clinical and include: (1) pain aggravated by patient movement or light skin pinching over the affected area and (2) pain improvement following local anesthetic injection. In general, electromyography is not useful because it lacks adequate sensitivity (Knockaert, 1996).

In addition to physical examination, local injection of anesthetic agents with or without corticosteroids in most cases will improve pain. One- or 2-percent lidocaine and a 40 mg/mL concentration of triamcinolone can be combined in a 1:1 ratio. Less than half a milliliter is injected at each site. Additional treatments may include oral analgesics, biofeedback, and gabapentin. If conservative options fail to bring sufficient relief, neurolysis with injection of 5- to 6-percent absolute alcohol or phenol or surgical neurectomy may be required (Madura, 2005; Suleiman, 2001).

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BREAST DISEASE: INTRODUCTION

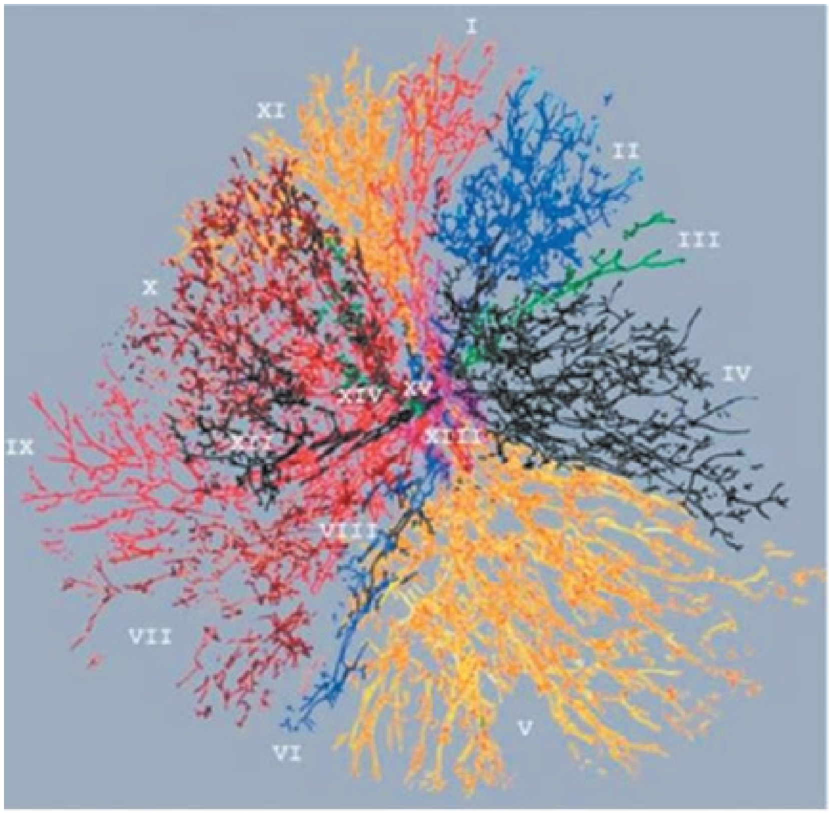
Breast disease in women encompasses a spectrum of benign and malignant disorders, which present most commonly as breast pain, nipple discharge, or palpable mass. The specific causes of these symptoms vary with patient age. Benign disorders predominate in young premenopausal women, whereas malignancy rates increase with advancing age. Evaluation of breast disorders usually requires the combination of a careful history, physical examination, imaging, and when indicated, biopsy.

ANATOMY

Ductal System

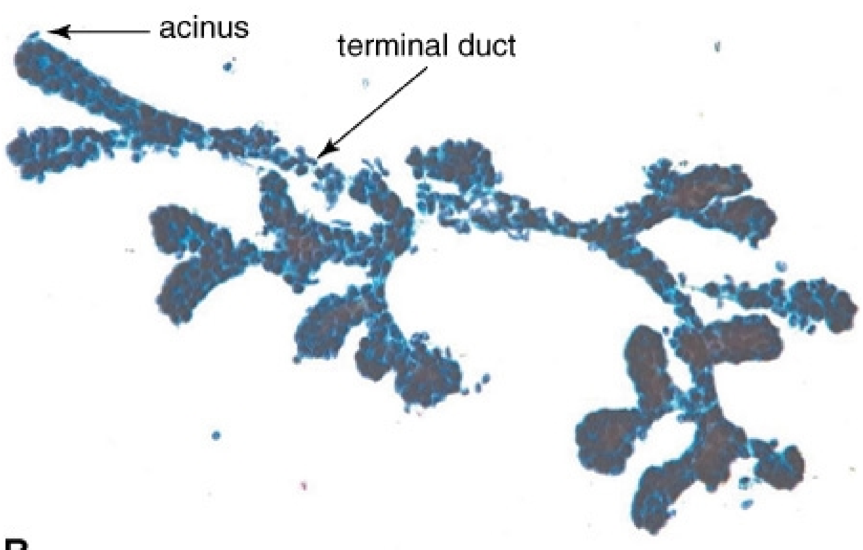
The glandular portion of the breast is comprised of 12 to 15 independent ductal systems that each drain about 40 lobules (Fig. 12-1). Each lobule consists of 10 to 100 milk-producing acini that drain into small terminal ducts (Parks, 1959). Terminal ducts drain into larger collecting ducts that merge into even larger ducts, which exhibit a saccular dilation just below the nipple called a lactiferous sinus (Fig. 12-2).

FIGURE 12-1



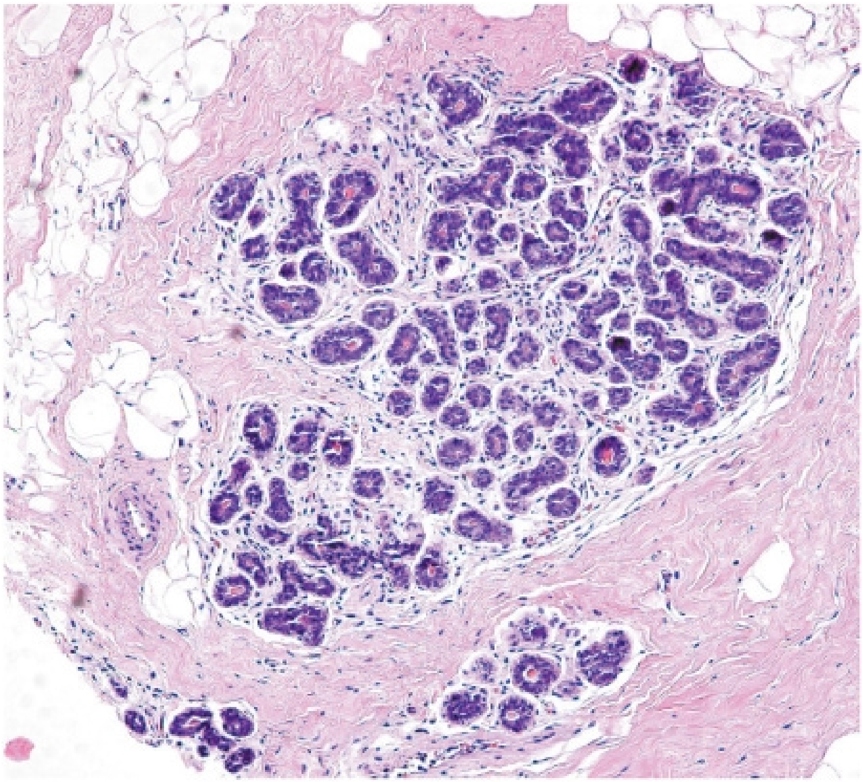
A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

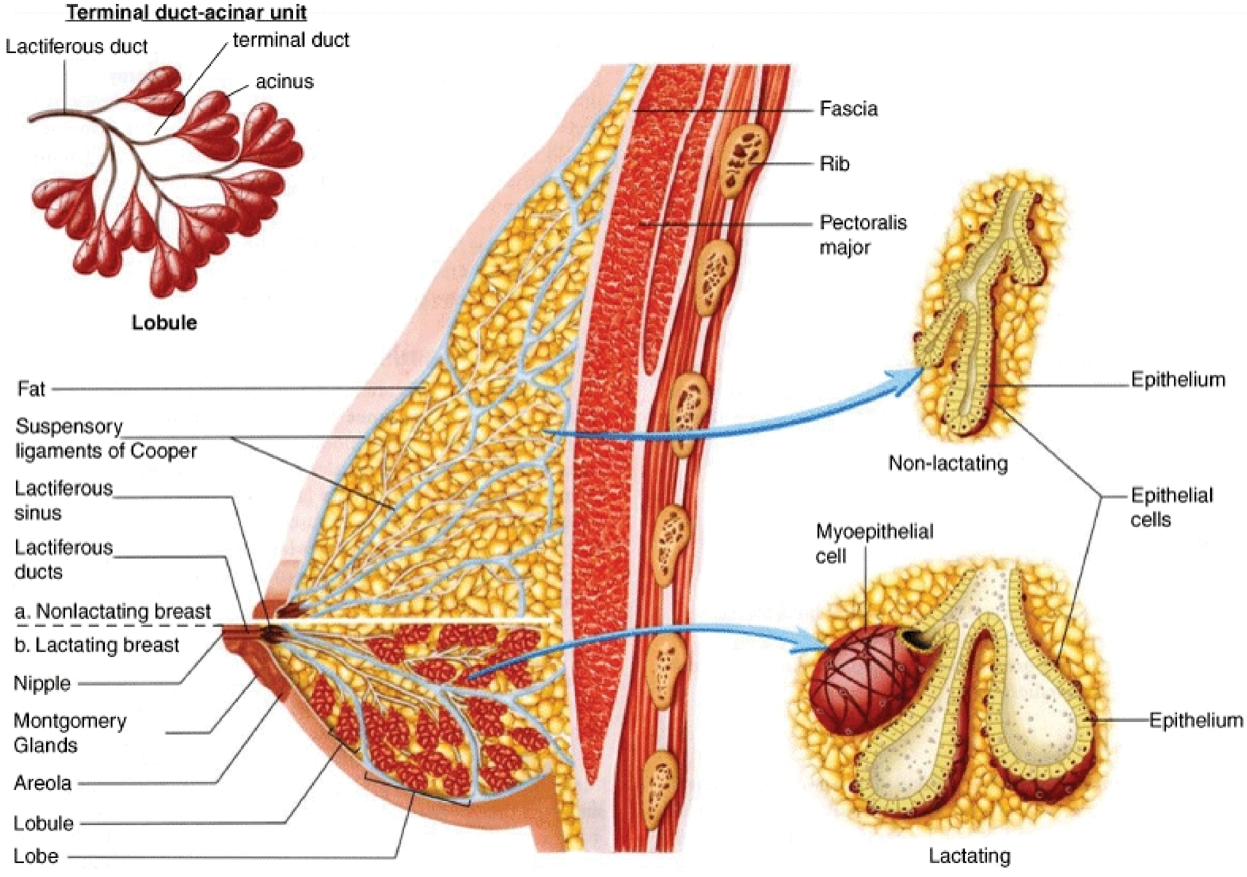


C

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

A. Ductal anatomy of the breast. *(From Going, 2004, with permission.)* **B.** Terminal duct-acinar structure from a fine-needle aspiration biopsy. **C.** Histology of a normal lobule.

FIGURE 12-2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Breast anatomy. *(From Seeley, 2006, with permission.)*

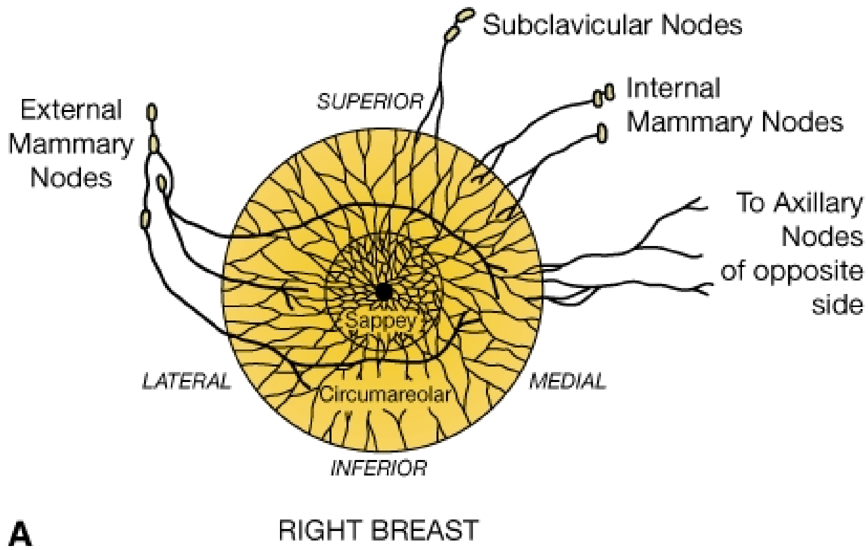
In general, only six to eight openings are visible on the nipple surface. These drain the dominant ductal systems, which account for about 80 percent of the breast's glandular volume (Going, 2004). Minor ducts either terminate just below the nipple surface or open on the areola near the base of the nipple. The areola itself contains numerous lubricating sebaceous glands, called Montgomery glands, which are often visible as punctate prominences.

In addition to epithelial structures, the breast is composed of varying proportions of collagenous stroma and fat. The distribution and abundance of these stromal components accounts for a breast's consistency when palpated and for its imaging characteristics.

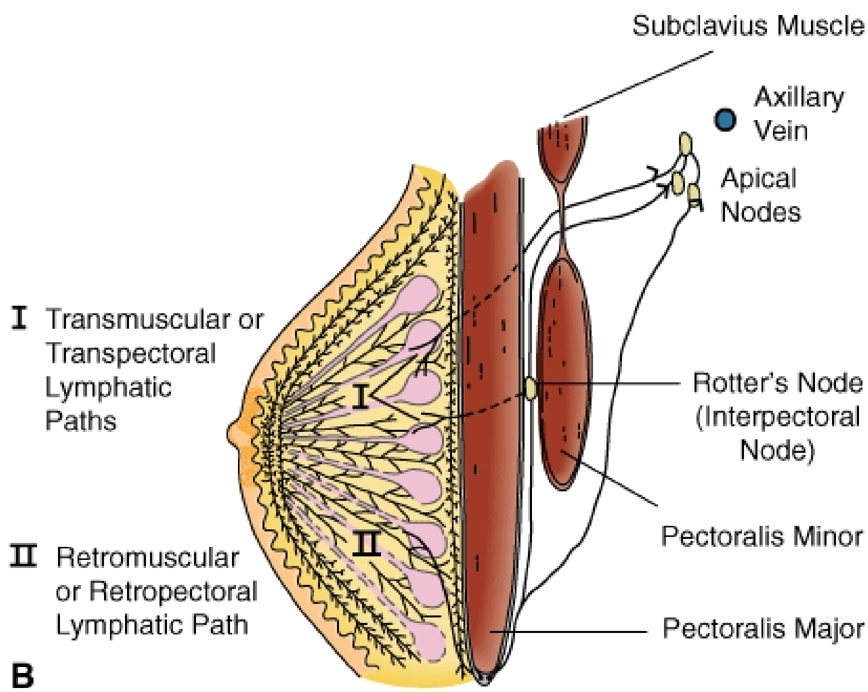
Lymphatic Drainage

Afferent lymphatic drainage of the breast is provided by dermal, subdermal, interlobar, and prepectoral systems (Fig. 12-3) (Grant, 1953). Each of these may be viewed as a lattice of valveless channels that interconnect with every other system and that ultimately drain into one or two axillary lymph nodes (the sentinel nodes). Because all of these systems are interconnected, the breast drains as a unit, and injection of colloidal dyes in any part of the breast at any level will result in accumulation of dye in the same one or two axillary sentinel lymph nodes. The axillary lymph nodes receive most of the lymphatic drainage of the breast, and consequently are the nodes most frequently involved with breast cancer metastases (Hultborn, 1955). However, there are also alternative drainage pathways that do not appear to interconnect with other networks and that drain directly into internal mammary, supraclavicular, contralateral axillary, or abdominal lymph node basins.

FIGURE 12-3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Lymphatic drainage of the breast. **A.** Accessory drainage pathways. **B.** Classic axillary drainage pathways. *(From Grant, 1953, with permission.)*

DEVELOPMENT AND PHYSIOLOGY

During fetal development, the primordial breast arises from the basal layer of the epidermis. Before puberty, the breast is a rudimentary bud comprised of a few branching ducts capped with alveolar buds, end buds, or small lobules (Osin, 1998). At puberty, usually between the ages of 10 and 13 years, ovarian estrogen and progesterone cooperate to direct organized communication between breast epithelial cells and mesenchymal cells, resulting in extensive branching of the ductal system and development of lobules (Ismail, 2003). Specific disorders of this development are discussed in Chapter 14, Breast Development and Disease. Final differentiation of the breast is mediated by progesterone and prolactin and is not completed until the first full-term pregnancy (Grimm, 2002; Ismail, 2003).

During the reproductive years, terminal ducts near the acini and the acini themselves are most sensitive to ovarian hormones and prolactin. Most forms of benign and malignant breast disease arise in these terminal duct-acinar structures. Breast epithelial cells proliferate during the luteal phase of the menstrual cycle when estrogen and progesterone levels are increased, and then undergo programmed cell death at the end of the luteal phase, when levels of these hormones decline (Anderson, 1982; Soderqvist, 1997). This effect is mediated by paracrine signaling induced by estrogen receptor activation and is associated with an increase in the water content of the extracellular matrix (Stoeckelhuber, 2002). This is often recognized as breast fullness and tenderness the week preceding menses.

At menopause, when ovarian estrogen production ceases, breast lobules involute, and the collagenous stroma is replaced by fat. Because estrogen receptor expression is negatively regulated by estrogen, there is an increase in estrogen receptor expression after menopause (Khan, 1997). Despite a decline in ovarian estrogen production, postmenopausal women continue to produce estrogen through the action of the enzyme aromatase, which converts adrenal androgens to estrogen (Bulun, 1994). Aromatase is found in fat, muscle, and breast tissue.

EVALUATION OF A BREAST LUMP

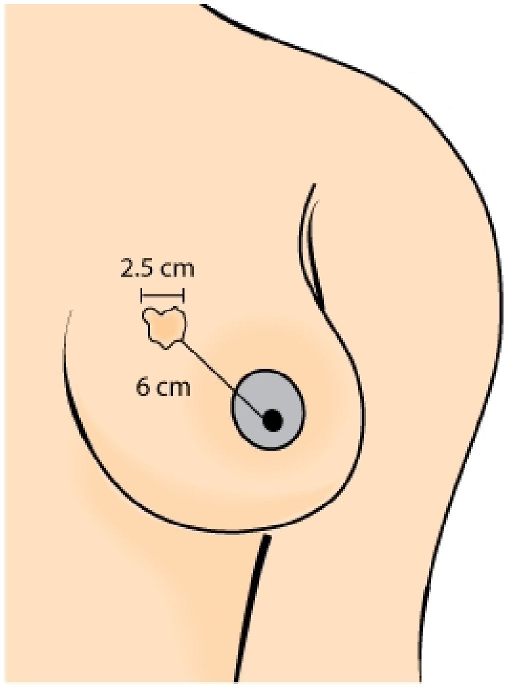
It is not possible to distinguish benign from malignant or cystic from solid breast masses by clinical examination. However, findings from clinical examination, interpreted in conjunction with imaging and pathology (the triple test), contribute significantly to management decisions (Hermansen, 1987).

Physical Examination

The breast is comma shaped, and the comma's tail corresponds to the axillary tail of Spence. This extension can be large, especially during pregnancy and lactation, and is frequently mistaken for an axillary mass.

Clinical examination of the breast begins with inspection of the breast to determine whether there is dimpling, nipple retraction, or skin changes. This examination is described further in Chapter 1. The presence and character of expressible nipple discharge is recorded. In addition, the location of a mass is specifically documented according to its clock position and then measured along the long axis using a ruler or caliper (Fig. 12-4). The distance from the center of the nipple to the center of the mass is specified. Since many health care providers are typically involved in the evaluation and management of the same breast mass, the most useful entry in the clinical record will define the location and size of the mass (e.g., right breast, 2-cm mass, 3:00, 4 cm from the nipple). Although clinical examination alone can never exclude malignancy, noting that a mass has benign features such as smoothness, roundness, and mobility will factor into the ultimate decision to excise or observe a lesion. Evaluation should also include careful examination of the axillae, infraclavicular fossa, and supraclavicular fossa (see Chap. 1, Lymph Node Evaluation).

FIGURE 12-4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Recording the location of a breast mass as "Left breast, 2.5-cm mass, 2:00, 6 cm FN". FN = from the nipple.

Diagnostic Imaging

Diagnostic imaging of a suspected mass may begin with mammography that includes magnification, extra compression, or extra views beyond the usual medial lateral oblique and cranial caudal views that are typically used for screening. Unlike screening mammography, diagnostic mammography may be appropriate for women of any age. In addition, sonography is invaluable for determining whether a mass is cystic or solid and is a component of most diagnostic imaging algorithms. Certain features of solid masses, such as irregular margins, internal echoes, or a width-to-height ratio <1.7 may suggest malignancy (Stavros, 1995).

BREAST IMAGING REPORTING AND DATA SYSTEM

Diagnostic imaging results should be summarized according to the Breast Imaging Reporting and Data System (BI-RADS) classification (Table 12-1) (D'Orsi, 1998). Lesions that are graded BI-RADS 5 are highly suggestive of malignancy, and ≥95 percent of these are ultimately proved to be cancerous. Decreasing numerical grades are associated with diminishing probability of malignancy.

Table 12-1 Breast Imaging Reporting and Data System (BI-RADS)		
BI-RADS Category	**Description**	**Examples**
0	Additional views or sonography required	Focal asymmetry, microcalcifications, or a mass identified on a screening mammogram
1	No abnormalities identified	Normal fat and fibroglandular tissue
2	Not entirely normal, but definitely benign	Fat necrosis from a prior excision, stable biopsy-proven fibroadenoma, stable cyst
3	Probably benign	Circumscribed mass that has been followed for <2 years
4A	Low suspicion for malignancy, but intervention required	Probable fibroadenoma, complicated cyst
4B	Intermediate suspicion for malignancy, intervention required	Partially indistinctly marginated mass otherwise consistent with a fibroadenoma
4C	Moderate suspicion, but not classic for carcinoma	New cluster of fine pleomorphic calcifications, ill-defined irregular solid mass
5	Almost certainly malignant	Spiculated mass, fine linear and branching calcifications
6	Biopsy-proven carcinoma	Biopsy-proven carcinoma

Breast Biopsy

Evaluation of a solid breast mass is completed by needle biopsy. These biopsies should be performed after an imaging test or a minimum of 2 weeks prior to an imaging test, as resulting tissue trauma can produce image artifacts that simulate malignancy (Sickles, 1983). Options include fine-needle aspiration (FNA) biopsy or core-needle biopsy (Boerner, 1999). The trend in recent years has been to prefer core-needle biopsy (Tabbara, 2000). Although FNA takes less time to perform and is less expensive than core-needle biopsy, it is less likely to provide a specific diagnosis and has a higher insufficient sample rate (Shannon, 2001). Fine-needle aspiration retrieves clusters of epithelial cells that may be interpreted as benign or malignant, but cannot reliably differentiate between benign proliferative lesions and fibroepithelial neoplasms or between ductal carcinoma in situ and invasive cancer (Boerner, 1999; Ringberg, 2001).

In contrast, core-needle biopsy is performed using an automated device that takes one core at a time, or using a vacuum-assisted device that once initially positioned, delivers multiple cores. Needle biopsy of solid masses is generally preferred prior to excision, as the results of the biopsy contribute significantly to surgical planning (Cox, 1995).

Triple Test

The combination of clinical examination, imaging, and needle biopsy is called the *triple test* . When all three assessments suggest a benign lesion or all three suggest a breast cancer, the triple test is said to be concordant. A concordant benign triple test is >99 percent accurate, and breast lumps in this category can be followed by clinical examination alone at 6-month intervals (Table 12-2). If any of the three assessments suggests malignancy, the lump should be excised regardless of results from the other two. It is always appropriate to offer excision of a fully evaluated breast lump, even after a benign concordant triple test, as breast lumps can be a source of significant anxiety.

Table 12-2 Performance Characteristics of the Concordant Triple Test[a]						
Citation	Number	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
Hermansen, 1987	458	1.00	0.74	0.64	1.00	0.82
Kreuzer, 1976	240	0.99	0.99	0.99	0.99	0.99
Kaufman, 1994	159	1.00	0.98	0.98	1.00	0.99
Hardy, 1990	116	0.98	0.53	0.68	0.97	0.76
Thomas, 1978	108	0.98	1.00	1.00	0.98	0.99
Butler, 1990	86	1.00	0.52	0.97	1.00	0.98
Du Toit, 1992	73	1.00	1.00	1.00	1.00	1.00

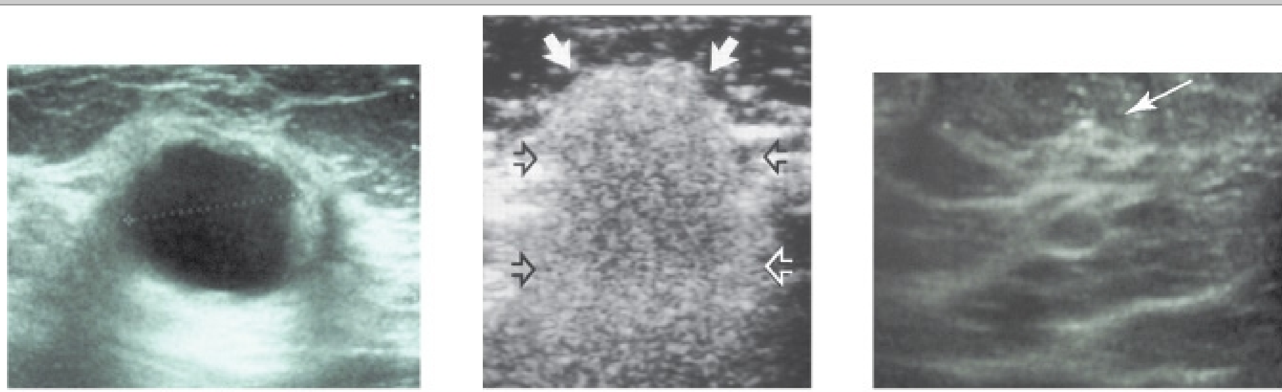
[a] Cytologic diagnoses of "definitively malignant" and "suspicious for malignancy" are considered positive. The triple test includes clinical examination, imaging, and needle biopsy. Only cases that were malignant by all three tests, or benign by all three tests are included in the calculations.

Cysts

Most breast cysts arise from apocrine metaplasia of lobular acini. They are generally lined by a single layer of epithelium that ranges from flattened to columnar. One autopsy series that included 725 women reported microcysts in 58 percent and cysts >1 cm in 21 percent (Davies, 1964). The incidence of breast cysts peaks between 40 and 50 years, and it has been estimated that the lifetime incidence of palpable breast cysts is approximately 7 percent (Haagensen, 1986b).

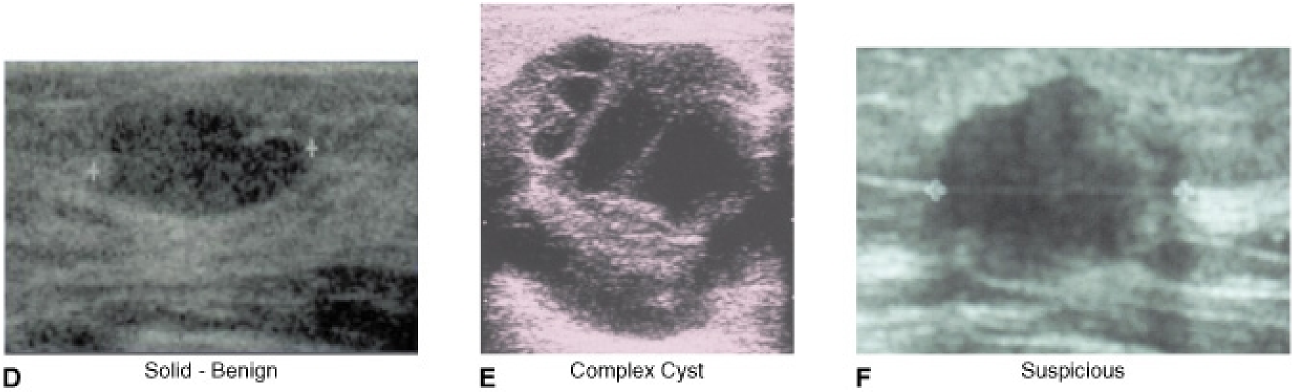
Breasts cysts are diagnosed and classified by sonographic examination. There are three types of cysts: simple, complicated, and complex (Berg, 2003). Simple cysts are sonolucent, have a smooth margin, and show enhanced through-transmission (Fig. 12-5). These lesions do not require special management or monitoring, but they may be aspirated if painful. Recurrent cysts can be re-imaged and re-aspirated, but recurrent symptomatic cysts are best managed by excision.

FIGURE 12-5



A Simple Cyst B Silicone C Fibroglandular Ridge

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Sonographic appearance of palpable breast masses. **A.** Simple cyst. **B.** Silicone granuloma. **C.** Fibroglandular ridge. **D.** Fibroadenoma. **E.** Complex cyst. **F.** Cancer.

Complicated cysts show internal echoes with sonography and can sometimes be indistinguishable from solid masses. Internal echoes are usually caused by proteinaceous debris, but all complicated cysts should be aspirated. The aspirated material may be submitted for culture if it is purulent, or for cytology if there are worrisome clinical or imaging features. If the sonographic abnormality does not resolve completely with aspiration, a core-needle biopsy is usually performed.

Complex cysts show septa or intracystic masses on sonographic evaluation. An intracystic mass usually represents a papilloma, but medullary carcinoma, papillary carcinoma, and some infiltrating ductal carcinomas can present as complex cysts. Although some have advocated core-needle biopsy for the evaluation of complex cysts, this procedure can decompress a cyst making it difficult to localize at the time of surgery. Additionally, papillary lesions diagnosed by needle biopsy will require excision. Thus, it seems reasonable to recommend excision of all complex cysts.

Fibroadenoma

Fibroadenomas represent a focal developmental abnormality of a breast lobule and as such are not true neoplasms. Histologically, fibroadenomas are comprised of glandular and cystic epithelial structures surrounded by a cellular stroma. Fibroadenomas account for 7 to 13 percent of breast clinic visits and had a prevalence of 9 percent in one autopsy series (Dent, 1988; Franyz, 1951). They often present in adolescence, are recognized most frequently in premenopausal women, and usually spontaneously involute at menopause.

Fibroadenomas classified as benign concordant by the triple test can be safely followed without excision. Because some fibroadenomas may grow large, and because benign phylloides tumors are often indistinguishable from fibroadenomas by imaging and needle biopsy, a fibroadenoma that is growing should be excised.

Phylloides Tumors

Histologically, phylloides tumors are similar to fibroadenomas in that epithelial-lined spaces are surrounded by cellular stroma. However, with phylloides tumors, the stromal cells are monoclonal and neoplastic. Phylloides tumors are classified as benign, intermediate, or malignant, based on the degree of stromal cell atypia, number of mitoses, tumor margin characteristics, and abundance of stromal cells (Oberman, 1965). Phylloides tumors account for less than 1 percent of breast neoplasms, and the median age at diagnosis is 40 years (Haagensen, 1986a; Reinfuss, 1996).

Malignant phylloides tumors can metastasize to distant organs, with lung being the primary site. Chest radiographs or chest computed-tomography (CT) scanning are appropriate staging tests for malignant cases. Phylloides tumors rarely metastasize to lymph nodes, thus axillary staging is not required unless there are clinically positive nodes (Chaney, 2000).

Treatment consists of wide local excision with a minimum 1-cm margin. Mastectomy may be required to achieve this margin, as the

median tumor size at presentation is 5 cm. Local recurrence rates for completely excised tumors range from 8 percent for benign lesions to 36 percent for malignant lesions (Barth, 1999).

NIPPLE DISCHARGE

Fluid can be expressed from the nipple ducts of at least 40 percent of premenopausal women, 55 percent of parous women, and 74 percent of women who have lactated within 2 years (Wrensch, 1990). The fluid generally issues from more than one duct and may range from milky white to dark green or brown. Green coloration is related to the content of cholesterol diepoxides and is not suggestive of underlying infection or malignancy (Petrakis, 1988).

Multiduct discharges that are elicited only following manual expression are considered physiologic and do not require additional evaluation. However, spontaneous discharges should be considered pathologic and merit evaluation (Fig. 12-6). Spontaneous milky nipple discharge, also called galactorrhea, may result from a variety of causes (Tables 12-3 and 12-4) (see Chap. 15, Etiology of Hyperprolactinemia). Pregnancy is another frequent cause of new-onset spontaneous discharge, and a bloody multiduct discharge during pregnancy is not uncommon.

Table 12-3 Causes of Galactorrhea
Physiologic conditions (14%) ■ Pregnancy and postpartum state ■ Breast stimulation ■ "Witch's milk" in neonates
Neoplastic processes (18%) ■ Pituitary adenoma (prolactinoma) ■ Bronchogenic carcinoma ■ Renal adenocarcinoma ■ Lymphoma ■ Craniopharyngioma ■ Hydatidiform mole ■ Hypernephroma ■ Mixed growth hormone-secreting and prolactin-secreting tumors ■ Null-cell adenoma
Hypothalamic-pituitary disorders (<10%) ■ Craniopharyngioma and other tumors ■ Infiltrative conditions ■ Sarcoidosis ■ Tuberculosis ■ Schistosomiasis ■ Pituitary-stalk resection ■ Multiple sclerosis ■ Empty-sella syndrome

Systemic diseases (<10%) ■ Hypothyroidism ■ Chronic renal failure ■ Cushing disease ■ Acromegaly
Medications and herbs (20%)
Chest wall irritation (<10%) ■ Irritating clothes or ill-fitting brassieres ■ Herpes zoster ■ Atopic dermatitis ■ Burns ■ Breast surgery ■ Spinal cord injury or surgery ■ Spinal cord tumor ■ Esophagitis ■ Esophageal reflux
Idiopathic (35%) ■ Hyperprolactinemia ■ Euprolactinemia

From Pena, 2001, with permission.

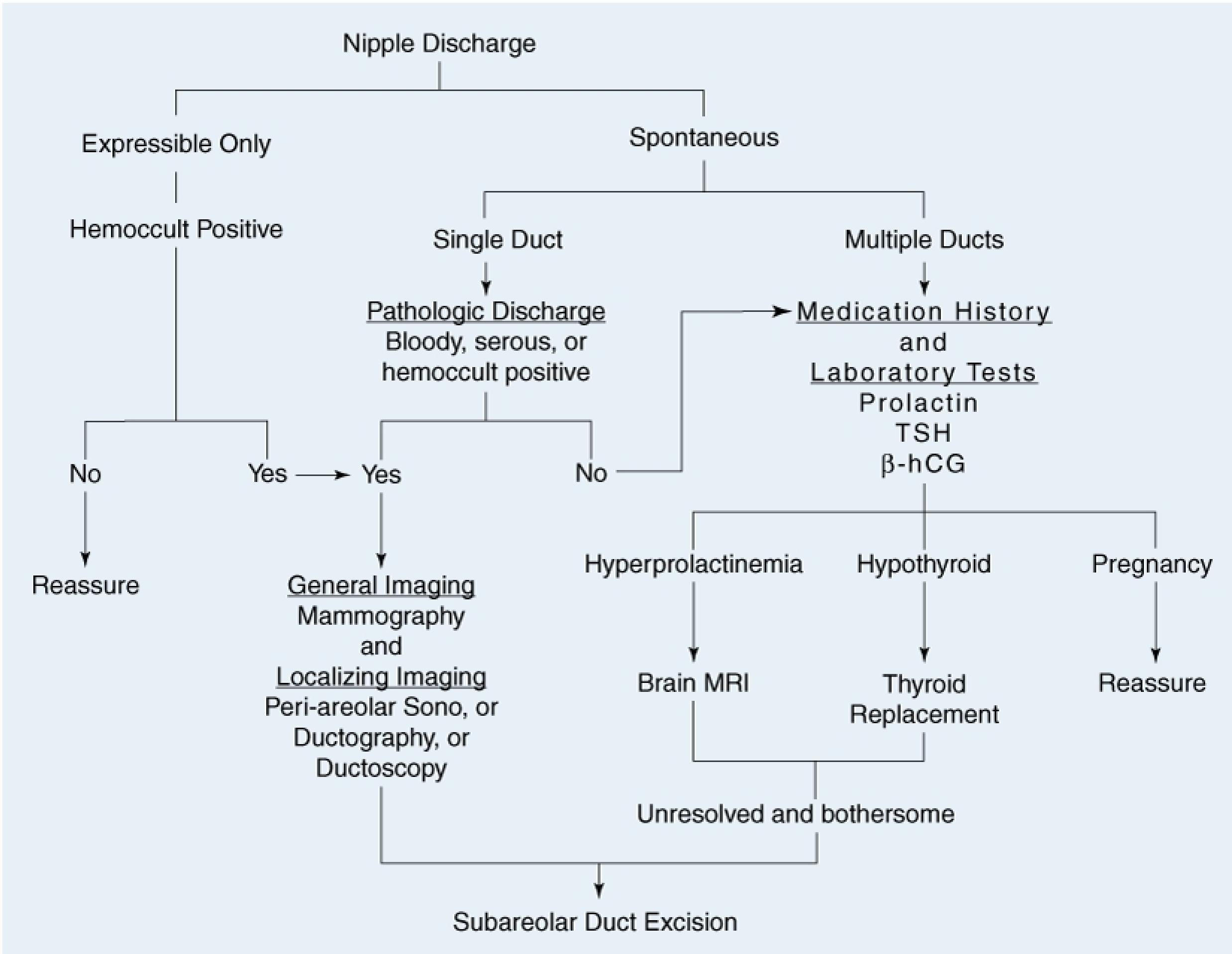
Table 12-4 Medications and Herbs Associated with Galactorrhea
Antidepressants and anxiolytics
Alprazolam (Xanax)
Buspirone (BuSpar)
Monoamine oxidase inhibitors
Moclobemide (Manerix; available in Canada)
Selective serotonin reuptake inhibitors
Citalopram (Celexa)
Fluoxetine (Prozacy)
Paroxetine (Paxil)

Sertraline (Zoloft)
Tricyclic antidepressants
Antihypertensives
Atenolol (Tenormin)
Methyldopa (Aldomet)
Reserpine (Serpasil)
Verapamil (Calan)
Antipsychotics
Histamine H_2 -receptor blockers
Cimetidine (Tagamet)
Famotidine (Pepcid)
Ranitidine (Zantac)
Hormones
Conjugated estrogen and medroxyprogesterone (Premphase, Prempro)
Medroxyprogesterone contraceptive injections (Depo-Provera)
Combination hormonal contraception
Phenothiazines
Chlorpromazine (Thorazine)
Prochlorperazine (Compazine)
Other drugs
Amphetamines
Anesthetics
Arginine
Cannabis
Cisapride (Propulsid)
Cyclobenzaprine (Flexeril)
Danazol (Danocrine)
Dihydroergotamine (DHE 45)

Domperidone
Isoniazid
Metoclopramide (Reglan)
Octreotide (Sandostatin)
Opiates
Rimantadine (Flumadine)
Sumatriptan (Imitrex)
Valproic acid (Depakene)
Herbs
Anise
Blessed thistle
Fennel
Fenugreek seed
Marshmallow
Nettle
Red clover
Red raspberry

From Pena, 2001, with permission.

FIGURE 12-6



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Diagnostic algorithm to evaluate nipple discharge hCG = human chorionic gonadotropin; MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

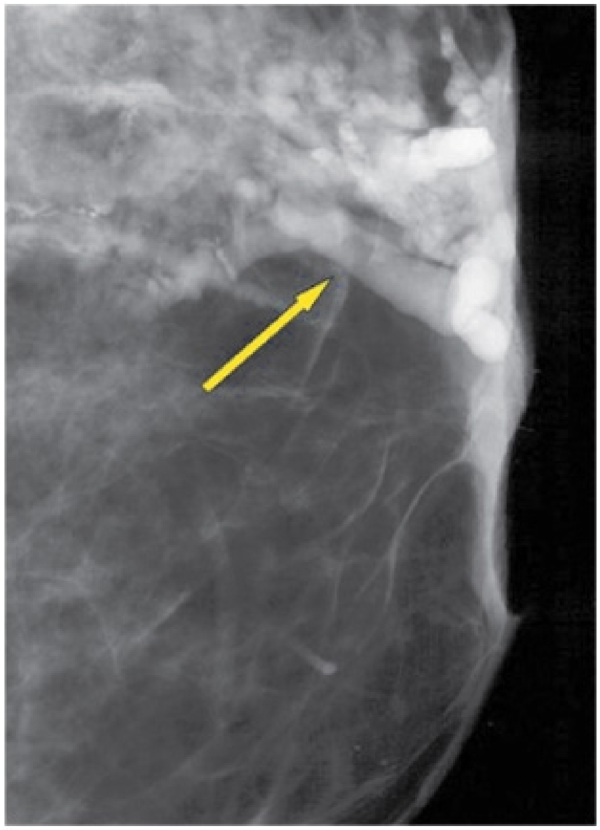
Pathologic nipple discharge is defined as a spontaneous single duct discharge that is serous or bloody. The rate of underlying malignancy ranges from about 2 percent for young women with no associated findings on imaging or physical examination to 20 percent for older women with associated findings (Cabioglu, 2003; Lau, 2005). Most pathologic nipple discharges are caused by benign intraductal papillomas, which are simple milk duct polyps (Urban, 1978). They arise in the major milk ducts, generally within 2 cm of the nipple, and contain a velvety papillary epithelium on a central fibrovascular stalk.

Evaluation of a pathologic nipple discharge begins with breast examination. Careful evaluation can frequently locate a trigger point on the areolar edge that elicits the discharge when pressed. Occult blood testing and microscopic examination of the discharge can provide additional information. A glass slide that has been touched to the discharge and immediately fixed in 95-percent alcohol may be used for cytologic assessment. Nipple fluid samples are acellular in 25 percent of cases and thus cannot exclude an underlying malignancy (Papanicolaou, 1958). However, malignant cells, if found, are highly correlated with an underlying cancer (Gupta, 2004).

Following these examinations, diagnostic mammography and an assessment of the subareolar ducts by ductography, mammary ductoscopy, or sonography is indicated. Diagnostic mammography is usually negative, but may occasionally identify an underlying ductal carcinoma in situ (DCIS). Mammary ductography, also known as galactography, requires cannulating the affected duct,

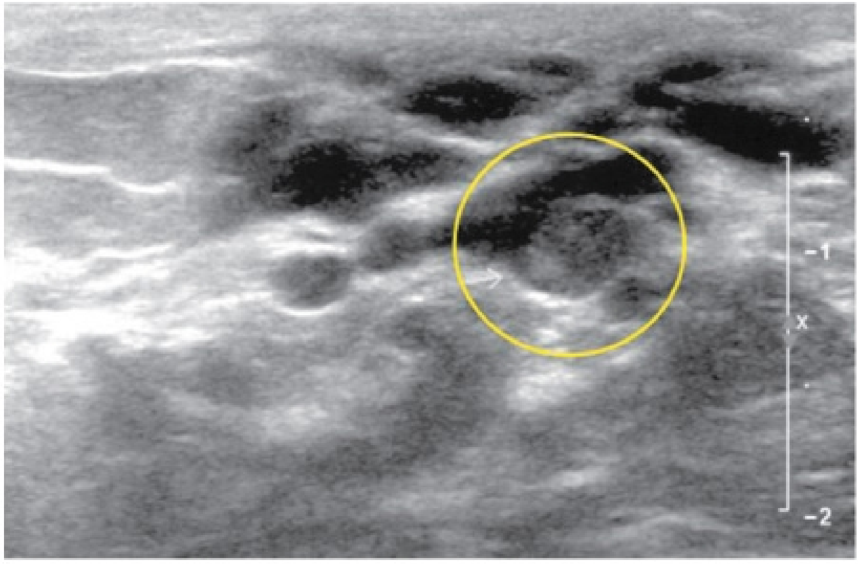
injecting radiocontrast, and then performing mammography (Fig. 12-7). In contrast, ductoscopy involves dilation and cannulation of the discharging breast duct, followed by passage of an endoscope measuring only 0.6 to 1.2 mm in diameter.

FIGURE 12-7



A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Imaging for a pathologic nipple discharge. **A.** Ductography shows dilated ducts and a filling defect (**arrow**). **B.** Periareolar sonogram with an intraductal mass, which is seen within the yellow circle.

An evaluation of the subareolar ducts, as described above, is required to localize an intraductal lesion for subsequent excision. However, pathologic nipple discharge is definitively diagnosed and treated by subareolar duct excision, which is also known as microductectomy (Locker, 1988). Subareolar duct excision can also be used to treat bothersome multiduct discharges not associated with prolactinoma.

BREAST INFECTIONS

Breast infections are generally divided into puerperal, which develop during pregnancy and lactation, and nonpuerperal.

Puerperal Infections

This staphylococcal infection of the breast is characterized by a warm, tender, diffuse erythema of the breast with systemic signs of infection such as fever, malaise, myalgias, and leukocytosis. It is successfully treated with oral or intravenous antibiotics, depending on the severity, but may also progress to form deep parenchymal abscesses that require surgical drainage. Sonographic examination is highly sensitive for identifying underlying abscesses if mastitis does not improve rapidly with antibiotics. Women with puerperal mastitis should continue to breast feed or breast pump during treatment to prevent milk stasis, which may contribute to infection progression (Thomsen, 1983). Cracked or excoriated nipples may provide a source of entry for bacteria and should be treated with lanolin-based lotions or ointments.

Focal mastitis may result from an infected galactocele. A tender mass will usually be palpable at the site of skin erythema. Needle aspiration of the galactocele and antibiotics are frequently all that is required, but recurrence or progression may mandate surgical drainage.

Nonpuerperal Infections

CELLULITIS

Uncomplicated cellulitis in a nonirradiated breast in a nonpuerperal setting is uncommon. Accordingly, its occurrence should prompt imaging and biopsies to exclude inflammatory breast cancer.

ABSCESS

Nonpuerperal breast abscesses are generally classified as peripheral or subareolar. Peripheral abscesses usually represent skin infections such as folliculitis or infection of epidermal inclusion cysts or Montgomery glands. These abscesses are all adequately treated by drainage and antibiotics.

In contrast, subareolar abscesses arise from keratin-plugged milk ducts directly behind the nipple. The abscess itself usually presents under the areola, and fistulous communications between multiple abscesses are common. Simple drainage is associated with a recurrence rate of 38 percent, thus effective treatment requires subareolar duct excision and complete removal of sinus tracts. In general, surgical drainage of breast abscesses should always be accompanied by biopsy of the abscess wall, as breast cancer occasionally presents as an abscess (Benson, 1989; Watt-Boolsen, 1987).

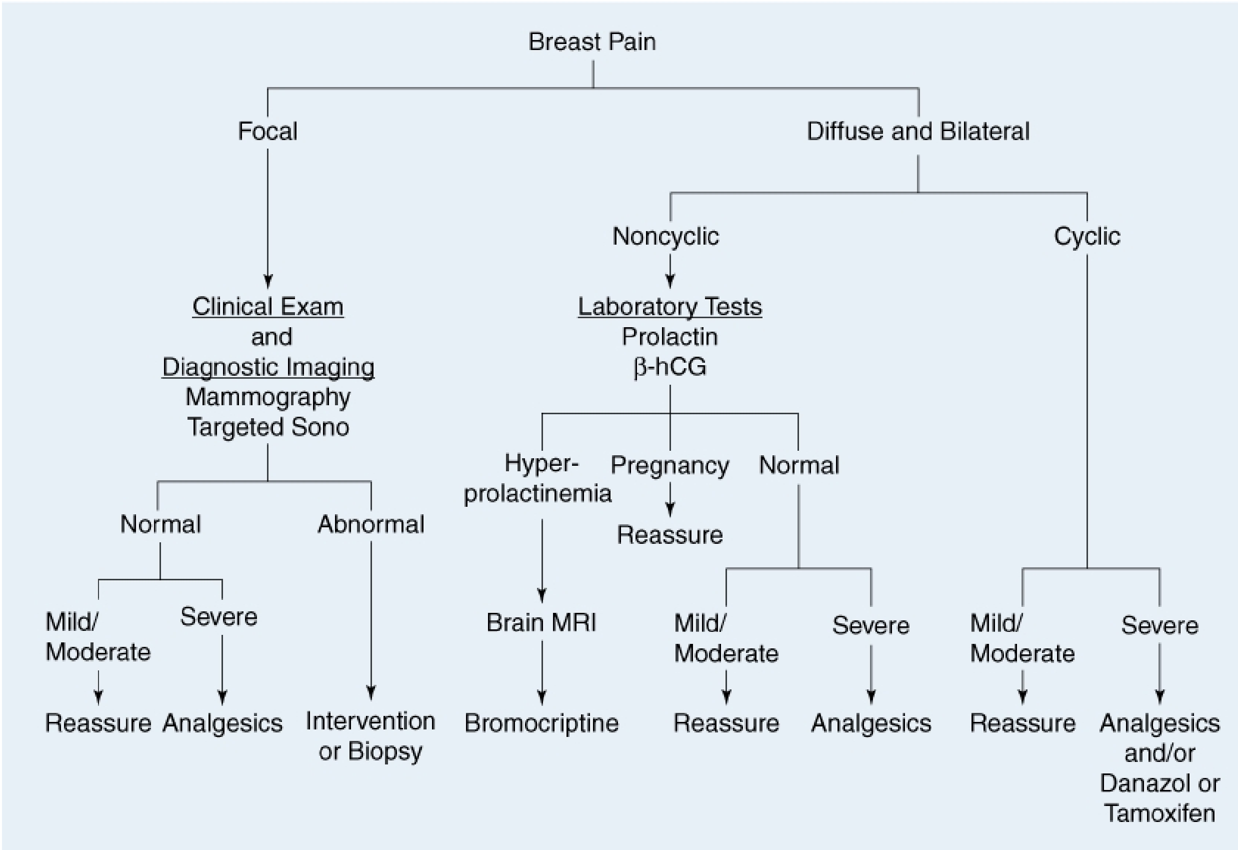
MASTALGIA

The prevalence of breast pain is 66 percent and is higher for women nearing menopause than for younger women (Euhus, 1997; Maddox, 1989). The precise etiology of mastalgia is unknown, but it is likely related to estrogen- and progesterone-mediated changes in interstitial water content, and therefore in interstitial pressure.

Mastalgia is generally classified as cyclic or noncyclic. Noncyclic mastalgia is often focal and shows no relationship to the menstrual cycle. Although focal mastalgia is frequently caused by a simple cyst, breast cancer occasionally presents as focal breast pain. Therefore, this complaint is evaluated by careful clinical examination, targeted imaging, and needle biopsy of any palpable or imaging abnormalities.

In contrast, cyclic mastalgia is usually bilateral, diffuse, and most severe during the late luteal phase of the menstrual cycle (Gateley, 1990). It remits with the onset of menstruation. Cyclic mastalgia requires no specific evaluation and is generally managed symptomatically with nonsteroidal anti-inflammatory agents (Fig. 12-8). A variety of other treatments have been proposed including bromocriptine, vitamin E, or oil of evening primrose, but outcomes are no better than placebo in the best randomized clinical trials, except for bromocriptine in the subset of women with elevated prolactin levels (Kumar, 1989; Mansel, 1990). For the most severe cases, several agent are effective when administered during the last 2 weeks of the menstrual cycle. These include: (1) danazol, 200 mg orally daily; (2) the selective estrogen receptor modifier, toremifene (Fareston, GTx, Memphis, TN), 20 mg orally daily, or (3) tamoxifen (Nolvadex, AstraZeneca, Wilmington, DE), 20 mg orally daily. Pregnancy must first be excluded and then avoided if these medications are used.

FIGURE 12-8



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Diagnostic algorithm to evaluate mastalgia. Oil of Evening Primrose or Vitamin E are frequently used for mild/moderate pain but the effects are no better than placebo. hCG = human chorionic gonadotropin; MRI = magnetic resonance imaging.

BENIGN PROLIFERATIVE BREAST DISEASE

Fibrocystic Change

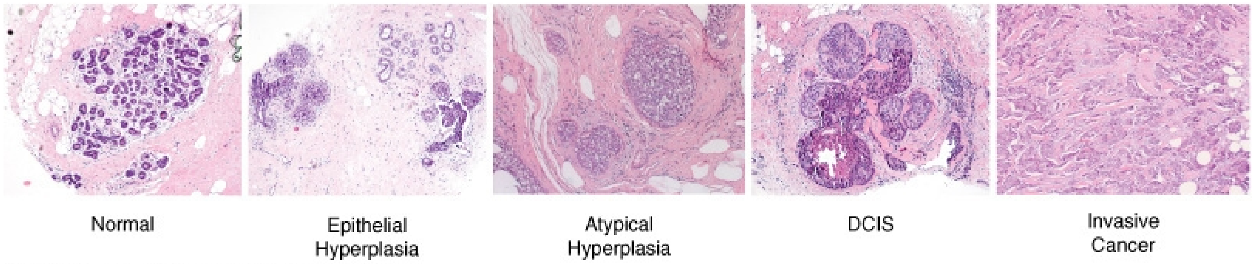
The primary tissue components of the breast are fat, fibrous stroma, and epithelial structures. The hormonally responsive component is the epithelium, but considerable paracrine communication exists between the epithelium and stroma. Hormonal stimulation may result in dilated fluid-filled lobular acini interpreted as microcysts on histologic sections and is usually accompanied by relative stromal abundance. This is commonly referred to as fibrocystic change. Depending on the particular pattern of epithelial structures and associated stroma, a breast may appear mammographically dense, feel nodular to palpation, or both. Fibrocystic change is generally classified as proliferative or nonproliferative according to the epithelial features of the process.

Ductal and Lobular Hyperplasia

For the most part, proliferative changes develop in the terminal ducts and acini of the lobules. These structures are usually lined by an inner layer of cuboidal luminal epithelial cells and an outer layer of myoepithelial cells. Proliferation of the luminal epithelial cells results in terminal ducts or acini with several layers of cells, which is referred to as ductal or lobular hyperplasia, respectively. As this process progresses the terminal ducts or acini become packed with cells, which begin to show nuclear atypia. This condition is referred to as atypical ductal hyperplasia (ADH) or atypical lobular hyperplasia (ALH), respectively. As more and more terminal ducts or acini become involved, the condition is recognized as ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS), depending on whether the cells are arising from the ducts or acini (Fig. 12-9) (Ringberg, 2001). In general, women with typical epithelial hyperplasia have a relative risk for breast cancer of about 1.5, whereas women with atypical hyperplasia have a relative

risk of approximately 4.5 (Dupont, 1993; Sneige, 2002).

FIGURE 12-9



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Histologic progression from normal breast tissue to cancer. DCIS = ductal carcinoma in situ.

These traditional histologic designations are gradually being replaced by a standardized scoring system that reflects the risk for subsequent breast cancer. Based on cell of origin, extent, and grade, the proposed categories include ductal intraepithelial neoplasia (DIN) low risk, 1, 2, and 3, and lobular intraepithelial neoplasia (LIN) 1, 2, or 3 (Bratthauer, 2002; Tavassoli, 2005).

LOBULAR CARCINOMA IN SITU

Lobular carcinoma in situ is not associated with any specific mammographic or palpable features and thus is only diagnosed incidentally. Classic LCIS has not traditionally been viewed as a direct precursor of breast cancer, but rather as a marker of increased breast cancer risk, because subsequent breast cancers develop with nearly the same frequency in both breasts (Chuba, 2005). The risk of subsequent breast cancer is approximately 1 percent per year but is modified upward by early age at diagnosis, family history of breast cancer, and extensive disease (Bodian, 1996).

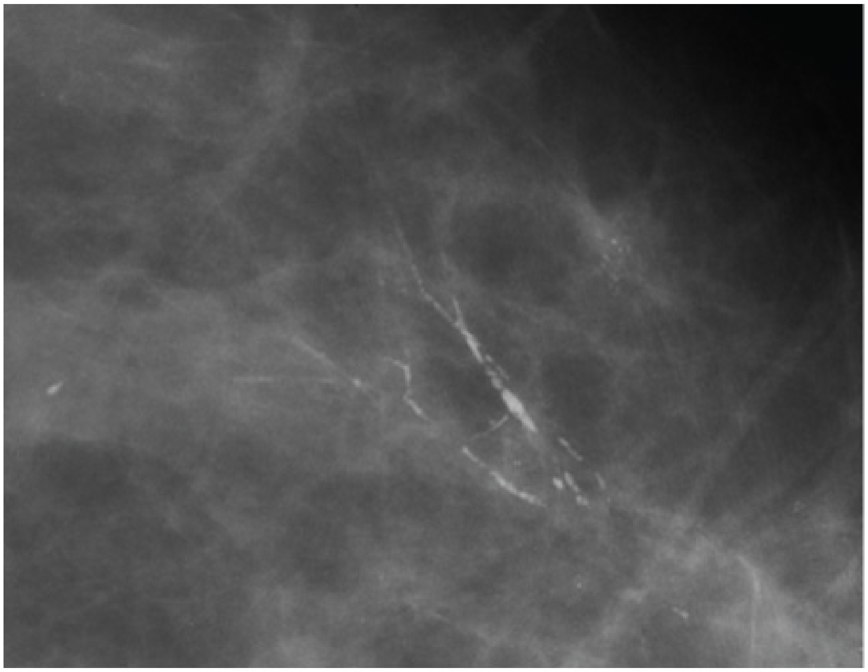
Lobular carcinoma in situ tends to be multifocal and bilateral, and therefore local excision with clear margins is frequently not possible and not necessary. Accordingly, management options include enhanced surveillance, chemoprevention, or bilateral prophylactic mastectomy. Enhanced surveillance may include twice-yearly clinical examinations and mammography alternating with screening magnetic resonance (MR) imaging. There are no data yet to show that screening MR imaging reduces breast cancer mortality among women with LCIS, but the infiltrating lobular cancers that can develop are frequently mammographically occult. Five years of tamoxifen has been shown to reduce breast cancer incidence by 56 percent in women with LCIS (Fisher, 1998). Raloxifene (Evista, Eli Lilly, Indianapolis, IN) may be an option for postmenopausal women (Vogel, 2006). Most women with LCIS do not opt for bilateral prophylactic mastectomy. However, for women with LCIS and a family history of breast cancer or for women who are continuing to require multiple biopsies, it is often a welcome solution.

DUCTAL CARCINOMA IN SITU

Ductal carcinoma in situ can be understood as a condition in which cancer cells fill portions of a mammary ductal system without invading beyond the duct's basement membrane (Ringberg, 2001). Although DCIS cells have accumulated many of the DNA changes common to invasive breast cancer, they lack certain critical changes that would permit them to persist outside of the duct (Aubele, 2002). Ductal carcinoma in situ is currently classified as stage 0 breast cancer.

The incidence of DCIS in the U.S. has increased in parallel with that of invasive breast cancer during the last two decades, but similar to invasive breast cancer, the incidence has plateaued during the last several years (Chuba, 2005). Ductal carcinoma in situ currently accounts for 25 to 30 percent of all breast cancers in the United States. It is most commonly diagnosed by screening mammography as it is frequently associated with pleomorphic, linear, or branching calcifications (Fig. 12-10).

FIGURE 12-10

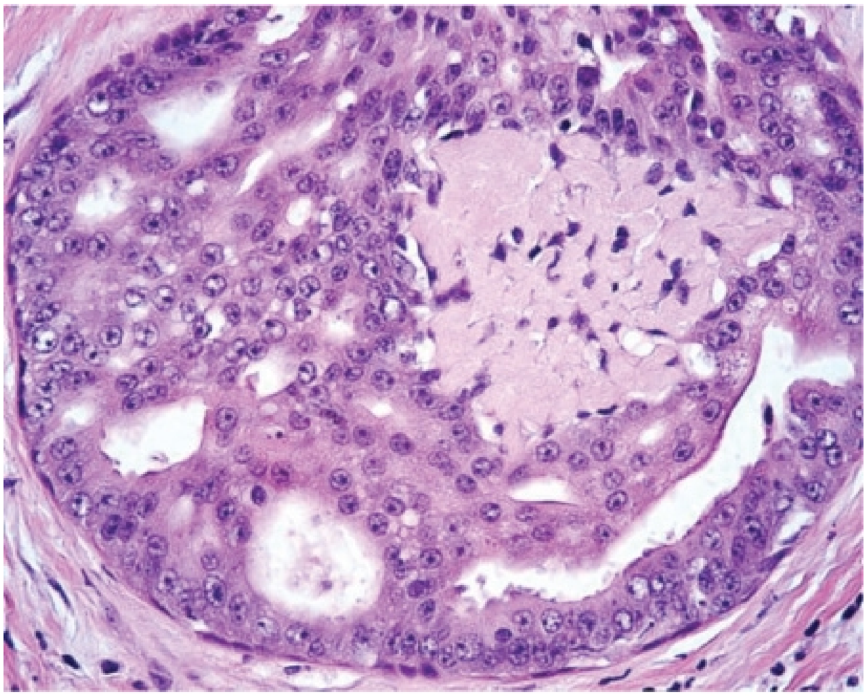


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Linear and branching calcifications associated with ductal carcinoma in situ. *(Courtesy of Dr. Phil Evans.)*

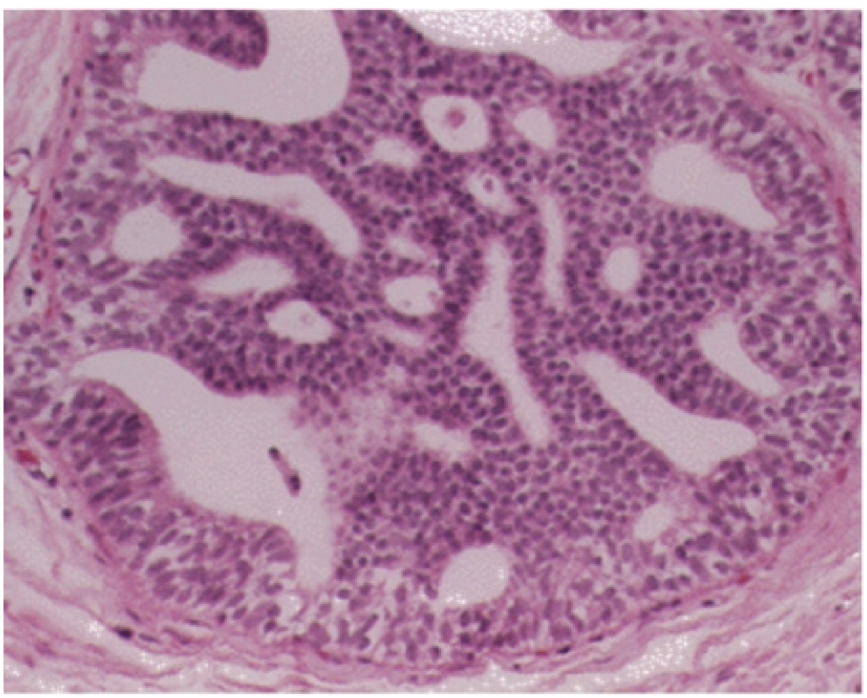
Ductal carcinoma in situ is classified by morphologic type, the presence or absence of comedonecrosis, and nuclear grade. The common morphologic types include cribriform, solid, micropapillary, and comedo (Fig. 12-11). Comedonecrosis appears as a necrotic eosinophilic core down the center of a duct packed with cancer cells. Of all of the classifying variables, nuclear grade is the most predictive for associated invasive cancer, extent of disease, and recurrence after treatment (Ringberg, 2001).

FIGURE 12-11



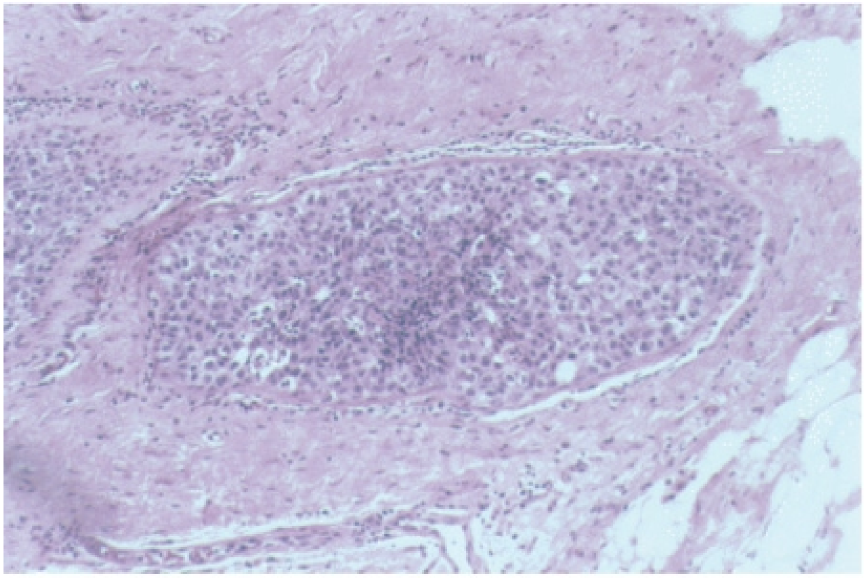
Comedo

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



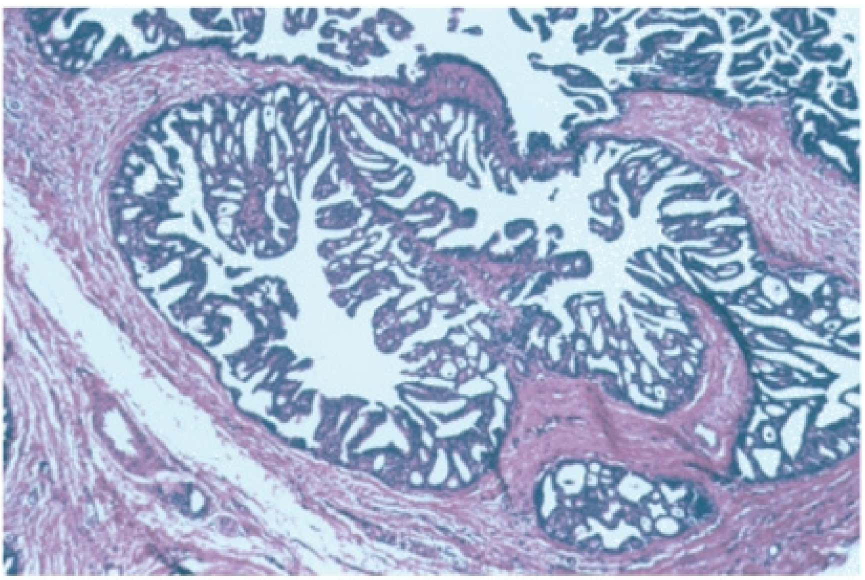
Cribriform

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



Solid

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



Micropapillary

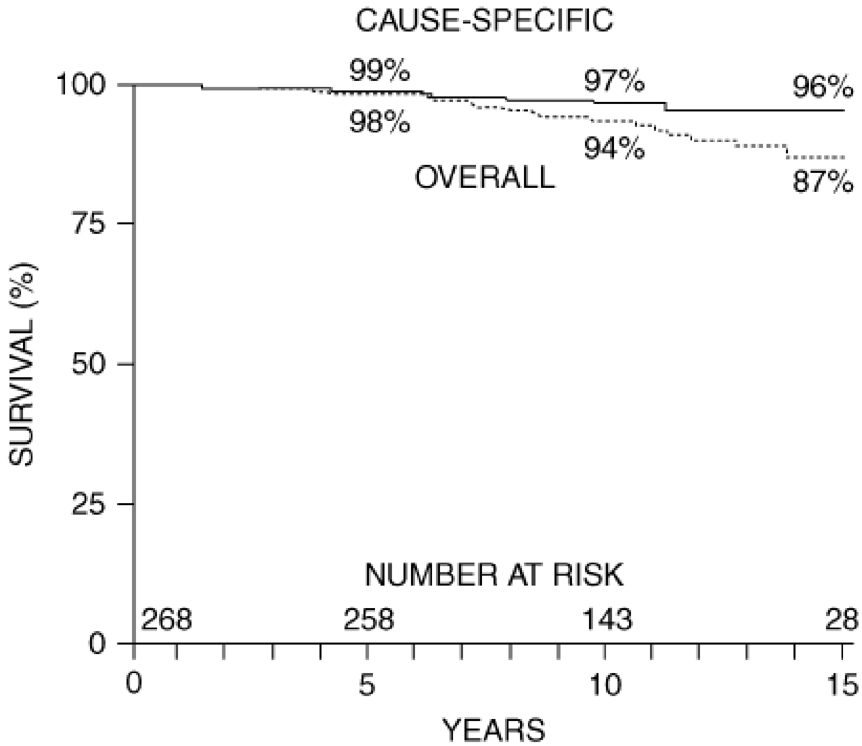
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Morphologic types of ductal carcinoma in situ (DCIS).

Incompletely treated DCIS may recur locally, and 50 percent of recurrences are associated with fully developed invasive breast cancer. The principal treatment of DCIS is wide excision with a negative margin. This may require mastectomy if DCIS is extensive or if there are other contraindications to breast conservation. When breast conservation is possible, postoperative breast irradiation will reduce the local recurrence rate from 18 percent to 9 percent and is considered standard adjuvant treatment (Fisher, 1993).

For those treated with breast conservation and radiation, breast cancerâ€"specific survival is 96 percent (Fig. 12-12) (Solin, 1996).

FIGURE 12-12



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Cause-specific and overall survival for ductal carcinoma in situ. *(From Solin, 1996, with permission.)*

Axillary staging is generally not included in the management of DCIS, although some have advocated sentinel node biopsy for large, high-grade DCIS diagnosed by needle biopsy and treated by lumpectomy, as occult invasive cancer is diagnosed in 10 percent (Wilkie, 2005). Sentinel lymph node (SLN) biopsy in conjunction with mastectomy is less controversial, as it is not possible to go back and perform SLN biopsy if an occult invasive cancer is diagnosed in this setting.

Five years of tamoxifen is recommended for estrogen receptorâ€"positive DCIS treated by breast conservation (Fisher, 1999). Although tamoxifen is not associated with a statistically significant improvement in overall survival, it does significantly reduce the incidence of ipsilateral invasive cancer and also reduces the risk of contralateral breast cancer.

Paget Disease of the Nipple

This type of DCIS presents as a focal eczematous rash of the nipple (Fig. 12-13). Ductal carcinoma cells, responding to chemoattractants secreted by cells in the dermis, migrate to the surface of the nipple inducing skin breakdown (Schelfhout, 2000). The condition is easily diagnosed histologically following excision of the affected nipple tip after nipple-areolar blockade using local anesthetic. Evaluation should also include careful clinical examination, as an associated mass is identified in about 60 percent of cases (Ashikari, 1970). Among those with no palpable abnormalities, mammography will show suspicious densities or calcifications in 21 percent (Ikeda, 1993). An underlying DCIS is identified in about two thirds of cases and an invasive cancer in approximately one third (Ashikari, 1970).

FIGURE 12-13

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

A. and **B.** Paget disease of the nipple. **C.** Benign reactive dermatitis. *(Courtesy of Dr. Marilyn Leitch.)*

Treatment includes wide excision with negative margins. Breast conservation, which requires central breast resection including the nipple-areolar complex and all identifiable underlying disease, is followed by postoperative breast irradiation (Bijker, 2001). Axillary staging by sentinel node biopsy is not required unless an invasive component is identified or total mastectomy is performed.

BREAST CANCER RISK FACTORS

The most profound breast cancer risk factor is female gender. In addition, the incidence of breast cancer, as for most other cancers, increases with advancing age. Other significant risk factors are related to reproductive variables, benign proliferative breast disease, and family history of breast or ovarian cancer.

Reproductive Factors

OVULATORY CYCLES

Ovulatory menstrual cycles exert stress on the breast epithelium by inducing proliferation in the late luteal phase. If conception does not occur, proliferation is followed by programmed cell death (Anderson, 1982; Soderqvist, 1997). Early age at menarche is associated with earlier onset of ovulatory cycles and increased breast cancer risk (den Tonkelaar, 1996; Vihko, 1986). Conversely, early menopause, whether it is natural or surgical, is associated with a reduced breast cancer risk (Kvale, 1988). Indeed, the lifetime number of ovulatory cycles is linearly related to breast cancer risk (Clavel-Chapelon, 2002). Pregnancy generates very high levels of circulating estradiol which is associated with a transient increase in short-term risk. But pregnancy also provides relief from ovarian cycling. Consequently, increasing parity is associated with reduced lifetime risk.

PREGNANCY

The breast is unique among all human organs in that it exists as a primordium for a decade or more before entering a highly proliferative state at menarche, and then does not fully mature until the first live birth. Immature breast epithelium is more susceptible to carcinogens than postlactational epithelium (Russo, 1996). Therefore, the longer a first live birth is delayed, the greater the breast cancer risk. Relative to nulliparity, first live births before the age of 28 years are associated with reduced breast cancer risk, whereas those thereafter are associated with increased risk (Gail, 1989). Both early age at first live birth and greater numbers of live births are associated with reduced breast cancer risk (Layde, 1989; MacMahon, 1970; Pathak, 1986; Pike, 1983).

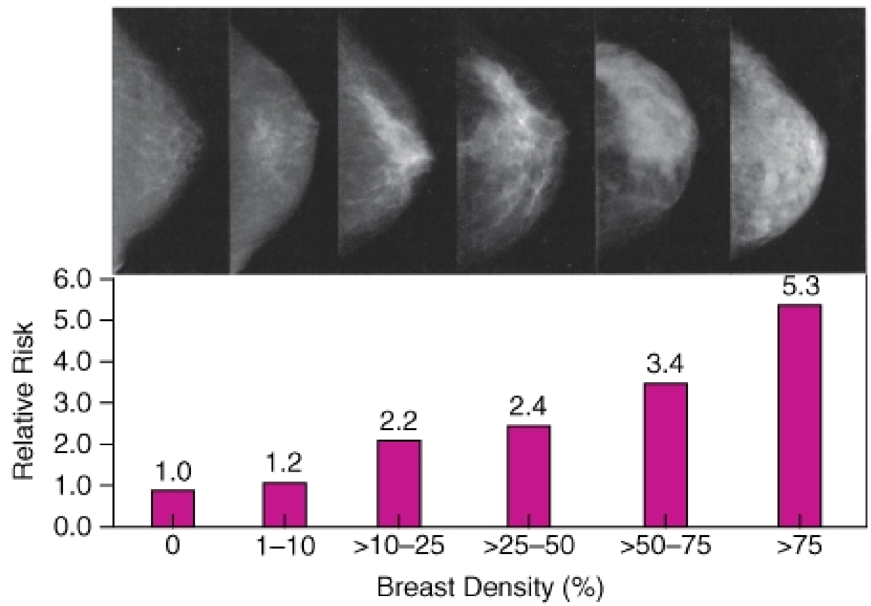
Benign Proliferative Breast Disease and Family History

As discussed above, benign proliferative breast disease is a marker of breast cancer risk, with relative risks ranging from 1.5 to 4.5 depending on whether epithelial cells are atypical or not (Dupont, 1993). A family history of breast cancer may also indicate an increased breast cancer risk, particularly with affected first-degree relatives (parents, siblings, or offspring), an early age at diagnosis, or bilateral breast cancer (Claus, 1994; Colditz, 1993).

Other Factors

Increased mammographic density is emerging as an important breast cancer risk factor. The incidence of breast cancer among women with almost entirely dense breasts is three- to sixfold greater than that of women with almost entirely fatty breasts, a relative risk approaching that conferred by a diagnosis of atypical ductal hyperplasia (Fig. 12-14) (Barlow, 2006; Boyd, 1995; Byrne, 1995; Ursin, 2003). Other minor breast cancer risk factors include alcohol consumption (>2 ounces per day), increased body mass index (for postmenopausal women only), increased height, and current use of combined estrogen-progestin hormone replacement therapy (Friedenreich, 2001; Lahmann, 2004; Macinnis, 2004; Smith-Warner, 1998; Writing Group for the Women's Health Initiative Investigators, 2002). Use of estrogen-only hormone replacement therapy has not been convincingly associated with an increased breast cancer risk (The Women's Health Initiative Steering Committee, 2004). In general, all of these risk factors are more prevalent in developed countries than less developed countries, Consequently, breast cancer is more common in industrialized cultures (Parkin, 2001).

FIGURE 12-14



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Relative risk of breast cancer increases with increasing mammographic breast density. *(From Santen, 2005, with permission.)*

Gail Model

In 1989, Gail evaluated more than a dozen potential breast cancer risk factors in a population of women undergoing screening mammography (Gail, 1989). Of these, age, age at menarche, age at first live birth, number of breast biopsies, and number of first-degree relatives with breast cancer emerged as the most important factors. The Gail model is a mathematical tool for calculating breast cancer risk based on these risk factors and has been independently validated (Costantino, 1999; Rockhill, 2001). A risk calculator is available to physicians through the National Cancer Institute website at http://www.cancer.gov/bcrisktool/ . However, shortcomings of the model include an inability to predict which women in a large group will actually develop breast cancer, failure to account for other risk factors (such as LCIS), and failure to adequately address family history factors. Although newer models, such as the Tyrer-Cuzick model, combine genetic risk factors with the established Gail factors and also include parity, age at menopause, history of LCIS or atypical ductal hyperplasia, height, and body mass index, but no other model has been independently validated as extensively as the Gail model (Tyrer, 2004). A recent modification of the Gail model includes a factor for mammographic density (Chen, 2006).

Breast Cancer Genetics

Nearly 30 percent of breast cancers have some familial component, but fewer than 10 percent are caused by inherited mutations in major breast cancer susceptibility genes (Antoniou, 2006; Lichtenstein, 2000). These genes operate in an autosomal dominant fashion and are involved in DNA repair or in controlling the cell cycle so that DNA can be repaired before the cell divides.

Family histories that suggest inherited susceptibility include early-onset breast cancer (<50 years), bilateral breast cancer, male breast cancer, multiple affected relatives in one generation, breast cancer in multiple generations, development of cancers that are known to be associated with a particular syndrome, and two or more cancers in one relative, especially if they develop at an early age. CancerGene is a widely used computer program for estimating gene mutation probabilities based on family history information (http://www4.utsouthwestern.edu/breasthealth/cagene). When possible, genetic testing is a powerful tool for determining who in the family is truly at high risk.

INHERITED BREAST-OVARIAN CANCER SYNDROME

This syndrome accounts for 5 to 7 percent of breast cancers (Malone, 2000). About 45 percent of individuals with this syndrome carry a *BRCA1* gene mutation and 35 percent a *BRCA2* mutation. Twenty percent of families with inherited breast-ovarian cancer syndrome test negative for *BRCA1* and *BRCA2* gene mutations, suggesting that other genes remain to be identified. Hallmarks of the BRCA1 form include early age at breast cancer diagnosis (median 44 years); high-grade, estrogen and progesterone receptorâ€"negative breast cancers; and associated ovarian cancer (Foulkes, 2004). The lifetime risk for breast cancer ranges from 35 to 80 percent, and for ovarian cancer 16 to 57 percent (Easton, 1995; Ford, 1994, 1998). Individuals who have developed both breast and ovarian cancer have an 86-percent probability of carrying a BRCA gene mutation (Cvelbar, 2005).

Women with *BRCA2* gene mutations develop breast cancer at about the same age as women with sporadic breast cancer, thus age at diagnosis is not usually a good criterion for recognizing this syndrome. Ovarian cancer is an associated cancer, but develops less frequently than it does in BRCA1 families. Males with *BRCA2* mutations develop breast cancer at about the same frequency as females without mutations, and 4 to 40 percent of male breast cancers are related to *BRCA2* mutations (Friedman, 1997; Thorlacius, 1996). Other associated cancers are listed in Table 12-5. Early premenopausal bilateral oophorectomy significantly reduces the incidence of both breast and ovarian cancer in women with inherited breast-ovarian cancer syndrome (Kauf, 2002; Rebbeck, 2002).

Table 12-5 Genetic Syndromes Associated with an Increased Risk of Breast Cancer

Syndrome Name	Genetic Mutation	Associated Disorders
Inherited breast-ovarian cancer	BRCA1, BRCA2	Cancers of the breast, ovary, pancreas, stomach, biliary system, and prostate and melanoma; male breast cancer for BRCA2
Li-Fraumeni	p53	Sarcoma, leukemia, melanoma and cancers of the breast, brain, adrenal cortex, pancreas, lung, cervix, and prostate
Cowden	PTEN	Breast: adenosis, fibrosis, hamartoma, fibroadenoma, and cancer (male and female); thyroid disease; ileum and colon hamartomatous polyps; facial tricholemmomas; macrocephaly; and oral papillomatosis
Peutz-Jegher	LKB1	Gastrointestinal hamartomatous polyps; cancers of the breast, small bowel, colon/rectum, pancreas, ovary, endometrium, cervix, lung, and testicle; and oral melanin pigmentation
$p16^{INK4a}$ and $p14^{ARF}$	$p16^{INK4a}$, $p14^{ARF}$	Leukemia/lymphoma, melanoma and cancers of the breast, pancreas, cervix, gallbladder, lung, larynx, prostate, liver, and intestine
Ataxia telangiectasia mutated	ATM	Lymphoma, leukemia, and breast cancer; cerebellar ataxia; telangiectasias; vitiligo; and cafÃ©-au-lait spots

CHK2	CHK2	Sarcoma, leukemia, melanoma and cancers of the brain, adrenal cortex, pancreas, lung, cervix, and prostate; male and female breast cancer

p16^{INK4a} and p14^{ARF} may also be known as dysplastic nevus syndromes.

Data compiled from Borg, 2000; Concannon, 2002; The Breast Cancer Linkage Consortium, 1999; The CHEK2-Breast Cancer Consortium, 2002; Evans, 1997; Lim, 2003; and Schrager, 1998.

Other recognized gene syndromes are associated with increased breast cancer risk (see Table 12-5). Their associated mutations affect genes involved with DNA repair, growth factor signaling, and cell-cell interactions. It is increasingly recognized that mutations in these genes, although rare, can cause predisposition syndromes that are very similar to those caused by *BRCA1* and *BRCA2* mutations.

Treatment options for breast cancers that arise in the context of an inherited predisposition syndrome are the same as for sporadic breast cancers. However, many of these women choose bilateral mastectomy, as the risk of an ipsilateral second primary breast cancer in a preserved breast can be as high as 3 to 4 percent annually, and the risk of a contralateral breast cancer is similar (Haffty, 2002; Seynaevea, 2004). Breast conservation is, however, an acceptable option for a highly motivated and well-informed patient (Robson, 1999).

BREAST CANCER SCREENING

Screening Mammography

This radiographic test is currently the best available and most thoroughly validated breast cancer screening test available. It has been evaluated in eight large randomized trials, the most recent of which was conducted in Canada in the 1980s (Begg, 2002). Controversies surrounding the benefits of screening mammography largely center on the impact of the test on breast cancerâ€"specific and overall mortality. However, at this time, it is generally accepted that for women aged 50 to 69 years, screening mammography reduces breast cancer mortality. Considerable uncertainty remains for women between the ages of 40 and 49, but several influential organizations including the American Cancer Society, the American Medical Association, and the American College of Radiology have recommended that yearly screening mammography begin at age 40. Recent improvements in screening mammography including digital mammography and computer-assisted diagnosis have improved the sensitivity of the test for some subgroups, challenging the contemporary relevance of older screening trials (Pisano, 2005).

It is important to recognize that most women with screen-detected abnormalities (~95 percent) do not have breast cancer, although the true-positive rate increases with increasing age (Feig, 2000). In addition, up to 25 percent of women diagnosed with breast cancer will have had a normal mammogram in the preceding 12 to 24 months.

Screening Sonography

This modality identifies mammographically occult breast cancer in less than 1 percent of women, but in one large study this translated into a 42-percent increase in screen-detected cancers (Gordon, 2002; Kolb, 2002). Screening sonography, however, is time consuming to perform and the accuracy is highly dependent on the operator.

Screening Magnetic Resonance Imaging

This screening option has recently been evaluated among genetically high-risk women. It is particularly attractive in this group of women, who develop breast cancer at a rate of 2 percent per year between the ages of 25 and 50, a time during which mammography sensitivity is reduced by dense breast tissue. In general, MR imaging shows higher sensitivity and specificity than mammography, but the test has been criticized for its expense and high false-positive rate (Leach, 2005; Stoutjesdijk, 2001; Tilanus-Linthorst, 2000; Warner, 2001). Nevertheless, for 100 women with a strong family history of breast cancer and a negative mammogram, nine abnormal MR imaging scans would be expected, and three of these would represent mammographically occult breast cancer.

Breast MR imaging requires specially trained radiologists, specialized equipment (a breast coil and a high-resolution magnet), and

is performed with and without intravenous gadolinium contrast (Orel, 2001). Areas of suspicious enhancement identified by MR imaging are evaluated by targeted sonographic examination and biopsied under sonographic guidance. If a lesion is not visible during sonography, then MR imagingâ€“guided core biopsy is performed.

Other Radiologic Tools

Other screening modalities in the developmental stage include breast tomosynthesis, sestamibi scanning, electrical impedance scanning, and thermography (Dobbins, 2003; Martin, 2002; Parisky, 2003; Sampalis, 2002). Of these, breast tomosynthesis warrants special mention, as it is likely to be adopted into the clinic in the near future. Tomosynthesis is a digital approach that obtains multiple images as the x-ray source and collector are rotated around the breast. Image slices are then reconstructed by a computer. This approach enhances calcifications and densities that would normally be obscured by intervening dense tissue.

Screening Physical Examination

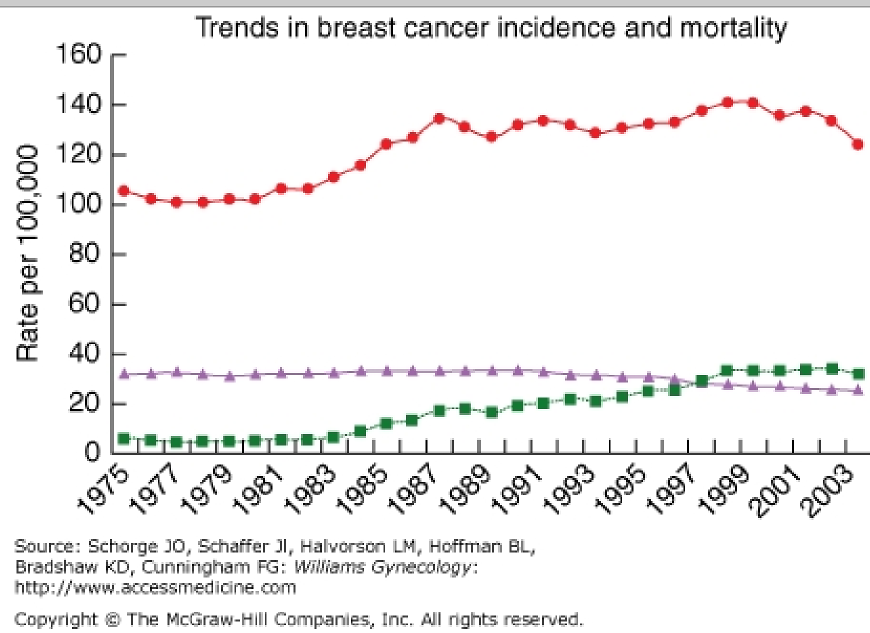
The value of a screening clinical breast examination (CBE) performed by health care providers should not be neglected (Jatoi, 2003). Four of the large randomized mammography trials collected information on CBE and found that 44 to 74 percent of the breast cancers were detected by this approach. Sensitivity and specificity were higher for CBE than mammography among young women.

Enthusiasm for breast self-examination (BSE) has diminished subsequent to publication of a very large randomized trial performed in Shanghai, China that found no improvement in mortality (Thomas, 2002). Although there is less interest in promoting systematic breast self-examination, it seems reasonable to encourage women to remain breast-aware.

INVASIVE BREAST CANCER

In the U.S., breast cancer is the most common cancer in women and the second most common cause of cancer-related mortality (second to lung) (Chuba, 2005). Although the incidence of breast cancer increased steadily in the U.S. through the 1980s and 1990s, it has leveled at about 125 cases per year per 100,000 and is declining for some ethnicities (Fig. 12-15).

FIGURE 12-15



Trends in breast cancer incidence and mortality in the United States. Curve of decreasing breast cancer rates in U.S. ● = incidence of invasive breast cancer; ■ = incidence in situ; ▲ = mortality. *(From the National Cancer Institute, 2005, with permission.)*

Tumor Characteristics

Primary cancers of the breast comprise 97 percent of malignancies affecting the breast, whereas 3 percent represent metastases from other sites. The most common of these, in descending order, are the contralateral breast, lymphoma, lung, and melanoma (Georgiannos, 2001). Cancers of mammary epithelial structures account for the vast majority of primary breast cancer. Infiltrating ductal carcinoma is the most common form of invasive breast cancer (~80 percent), and infiltrating lobular carcinoma is the second most common (~15 percent). Other malignancies such as phylloides tumors, sarcoma, and lymphoma comprise the remainder.

Apart from stage, the primary tumor characteristics that most influence prognosis and treatment decisions are hormone receptor status, nuclear grade, and Her-2/neu expression (Bast, 2001). Approximately two thirds of breast cancers are estrogen and progesterone receptor positive. This feature is generally associated with a better prognosis and more treatment options.

Her-2/neu is a membrane tyrosine kinase that cooperates with other Her-family receptors to generate proliferation and survival signals in breast cancer cells. Approximately 25 percent of breast cancers have increased expression of Her-2/neu (Masood, 2005). These cancers are usually sensitive to the humanized monoclonal antibody, trastuzumab (Herceptin, Genentech, South San Francisco, CA), which represents the first in a new class of targeted therapies (Plosker, 2006).

Recently, gene expression profiling has been used to classify individual tumors, and it is anticipated that in the future, individualized therapies will be selected based on the pattern of nuclear and growth factor receptors that are active in a given tumor (Habel, 2006; van de Vijver, 2002).

Breast Cancer Staging

Careful breast cancer staging is essential for predicting outcome, planning treatment, and comparing treatment effects in clinical trials. Each patient is assigned both a clinical and a pathologic stage. The clinical stage is based on clinical examination and radiographic findings, whereas a pathologic stage is based on actual tumor measurements and pathologic assessments of lymph nodes after primary surgery. Surgical staging of breast cancer is based on the TNM system, which includes primary tumor size (T), regional lymph node involvement (N), and presence of distant metastases (M) (Table 12-6). For patients with a clinically and sonographically negative axilla, sentinel lymph node biopsy has largely replaced complete axillary dissection for nodal staging (Giuliano, 1995; Lyman, 2005). Alternatively, axillary metastases may be diagnosed preoperatively by sonography-guided needle biopsy in 18 percent of patients with clinically negative axillae (Sapino, 2003).

Table 12-6 Breast Cancer Surgical Staging

T Stage		**Stage Grouping**			
Tis	In situ	0	Tis	N0	M0
T1	≤2 cm	I	T1	N0	M0
T2	>2 cm but ≤5 cm	IIA	T0	N1	M0
T3	>5 cm		T1	N1	M0
T4	Involvement of skin or chest wall or inflammatory cancer		T2	N0	M0
		IIB	T2	N1	M0
			T3	N0	M0
N Stage		IIIA	T0	N2	M0
N0	No lymph node involvement		T1	N2	M0
N1	1â€"3 nodes		T2	N2	M0

N2	4-9 nodes		T3	N1	M0
N3	≥10 nodes or any infraclavicular nodes		T3	N2	M0
		IIIB	T4	N0	M0
M Stage			T4	N1	M0
M0	No distant metastases		T4	N2	M0
M1	Distant mestastases	IIIC	Any T	N3	M0
		IV	Any T	Any N	M1

The most common metastatic site in breast cancer is the bone, and practice varies with respect to screening for metastatic disease. However, common screening modalities include CT of the chest, abdomen, and pelvis combined with bone scintigraphy or combined whole body positron emission tomography and CT (PET/CT) (Kumar, 2005). Bone scintigraphy is usually recommended in patients assessed by PET/CT, as PET/CT can miss osteolytic bone metastases.

Breast Cancer Treatment

Breast cancer is best treated in a multidisciplinary environment that includes surgeons, medical oncologists, and radiation oncologists. Surgery and radiation therapy are aimed at eliminating all local or regional tumor in a way that maximizes cosmetics and minimizes the risk of local or regional recurrence. There is some evidence that these local modalities reduce the risk of subsequent metastases and therefore impact survival (Early Breast Cancer Trialists Collaborative Group, 2005). However, a significant proportion of patients with apparently localized disease have tumor cells detectable in their blood or bone marrow at diagnosis, making systemic treatment with chemotherapy, hormone manipulation, or targeted therapies the primary approach for reducing the risk of metastases and death (Euhus, 2007).

SURGERY

Although Halstead revolutionized the treatment of breast cancer by demonstrating improved outcome for patients treated with radical mastectomy, results from recent randomized clinical trials have appropriately fostered a trend towards less aggressive surgery (Halstead, 1894). Specifically, it has been thoroughly documented that lumpectomy with postoperative radiation therapy results in the same breast cancerâ€"specific survival as total mastectomy (Fisher, 2002a, 2002b). During surgery, more extensive axillary lymph node dissection is indicated for patients with a positive sentinel node or with axillary disease diagnosed by needle biopsy (Lyman, 2005). The procedure results in lymphedema in 15 to 50 percent of women, depending on how it is measured (Morrell, 2005). It is also associated with persistent shoulder or arm symptoms in up to 70 percent (Kuehn, 2000). Following lumpectomy, whole breast irradiation is the standard, although preliminary data for accelerated partial breast irradiation are encouraging (Jeruss, 2006; Zannis, 2005).

CHEMOTHERAPY

In the past, adjuvant chemotherapy was reserved for patients with nodal metastases and was always given after definitive surgery. However, randomized prospective trials have shown that adjuvant chemotherapy improves survival for high-risk node-negative patients as well (Fisher, 2004; National Institutes of Health, 2000). More and more, however, the decision for chemotherapy is influenced by specific measures of tumor biology.

If used, adjuvant chemotherapy is usually administered after primary surgery but before radiation therapy. Neoadjuvant chemotherapy is given prior to definitive surgery and is gaining popularity. Neoadjuvant chemotherapy permits assessment of the sensitivity of a given tumor to the selected agents, and the tumor shrinkage that often results permits less aggressive surgery.

Modern breast cancer chemotherapy usually includes an anthracycline such as doxorubicin (Adriamycin), in conjunction with cyclophosphamide (Trudeau, 2005). Taxanes may replace anthracyclines in the near future, as they are less toxic and are

associated with equivalent or superior outcomes (Nabholtz, 2005). Chemotherapeutic agents are described more fully in Chapter 27.

HORMONAL THERAPY AND TARGETED THERAPIES

Adjuvant hormonal therapy is used for estrogen receptorâ€“positive tumors. Options include the selective estrogen receptor modifier, tamoxifen, in pre- or postmenopausal women or an aromatase inhibitor in postmenopausal women (Jaiyesimi, 1995; Kudachadkar, 2005). In postmenopausal women, most circulating estradiol is derived from the peripheral conversion of androgens by the enzyme aromatase. Administration of aromatase inhibitors reduces circulating estradiol to nearly undetectable levels in postmenopausal women. The addition of an aromatase inhibitor after tamoxifen is associated with a 23 to 39 percent improvement in disease-free survival and a nearly 50-percent reduction in contralateral breast cancer (Geisler, 2006).

Therapies that target specific biological pathways are becoming available. Trastuzumab is a humanized monoclonal antibody that is very effective against Her-2/neu overexpressing tumors, and bevacizumab (Avastin, Genentech, South San Francisco, CA), a vascular endothelial growth factor (VEGF) antagonist, is finding a place in the clinic (Gonzalez-Angulo, 2006; Rugo, 2004). In addition, dozens of other antibodies and small molecules that target growth factors and receptor tyrosine kinases or their intermediaries are currently being evaluated in clinical trials (Kaklamani, 2004).

SURVEILLANCE

Long-term surveillance of breast cancer patients after treatment includes periodic history and physical examination, both general and directed at eliciting signs or symptoms of recurrence. Women who elected breast conservation should be aware that the remaining breast tissue requires surveillance indefinitely, as ipsilateral second primary breast cancers develop at a rate of approximately 1 percent per year and contralateral breast cancers at approximately 0.7 percent per year (Fatouros, 2005; Fisher, 1984; Gao, 2003). Laboratory and imaging tests are obtained to further evaluate specific signs or symptoms. The use of screening tests other than mammography to identify asymptomatic recurrences is not recommended (Emens, 2003; Khatcheressian, 2006).

Inflammatory Breast Cancer

Inflammatory breast cancer accounts for about 6 percent of breast cancers, but its incidence is increasing (Chang, 1998). This cancer presents with skin changes that can range from a faint red blush to a flaming red rash associated with skin edema (peau d'orange change) (Fig. 12-16). It is distinguished from a neglected advanced primary breast cancer by its rapid onset and progression within just a few weeks. The cancer spreads rapidly throughout the entire breast and creates diffuse induration. As a result, the breast may enlarge to two to three times its original volume within weeks (Taylor, 1938).

FIGURE 12-16

A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photographs of inflammatory breast cancer. **A.** Subtle erythematous blush and edema in inflammatory breast cancer. **B.** Classic inflammatory breast cancer. *(Courtesy of Dr. Marilyn Leitch.)*

Although mastitis or even congestive heart failure can produce a similar clinical appearance, inflammatory breast cancer must be definitively excluded. This always includes diagnostic mammography and punch biopsy of the skin, but may require multiple biopsies and additional imaging tests such as MR imaging or sestamibi scanning. Treatment begins with induction chemotherapy, which is followed by modified radical mastectomy (total mastectomy and axillary dissection) and then postoperative chest wall irradiation with or without additional chemotherapy (Cariati, 2005). Five-year survival is 30 to 55 percent, which is significantly worse than for neglected advanced primary breast cancer (Brenner, 2002; Harris, 2003).

BREAST CANCER PREVENTION

Obesity and a sedentary life style are two modifiable risk factors that should be addressed in high- and lower-risk women. Although some studies have reported a reduced breast cancer risk among women consuming five or more servings a day of fresh fruits and vegetables, prospective studies have not convincingly linked any single dietary practice to breast cancer incidence (Gandini, 2000; Meskens, 2005). Regular physical activity is consistently associated with reduced breast cancer risk in clinical trials (Lee, 2003).

Women at high risk for breast cancer have three main options: (1) enhanced surveillance, (2) chemoprevention, or (3) prophylactic surgery. Enhanced surveillance usually consists of clinical examination every 6 months, alternating mammography with breast MR imaging or screening sonography. Enhanced surveillance can begin 10 years before the earliest age of breast cancer diagnosis in a family.

The U.S. Food and Drug Administration has approved tamoxifen for breast cancer chemoprevention in pre- or postmenopausal women 35 years or older with a 5-year Gail model risk ≥1.7 percent. Five years of tamoxifen is associated with a 49-percent reduction in breast cancer incidence, including both invasive breast cancer and DCIS (Fisher, 1998). However, tamoxifen is associated with an increased incidence of endometrial cancer and an increased risk of thromboembolic disease including deep vein thrombosis, pulmonary embolism, and stroke. Raloxifene is another selective estrogen receptor modulator that reduces the incidence of invasive breast cancer to the same extent as tamoxifen, but it does not reduce the risk of DCIS to the same extent (Vogel, 2006). Raloxifene has been associated with a lower risk of endometrial cancer and thromboembolic complications than tamoxifen. Raloxifene has not been evaluated in premenopausal women, although tamoxifen has.

Prophylactic surgery is usually reserved for women at very high risk for breast cancer. This includes women with inherited mutations in breast cancer predisposition genes and some women with LCIS, particularly if it is extensive or associated with a family history of breast cancer. Bilateral prophylactic oophorectomy performed in premenopausal women with BRCA gene mutations has been shown to reduce the risk of breast cancer by 50 percent and the risk of ovarian cancer by more than 90 percent (Eisen, 2005; Kauf, 2002; Rebbeck, 2002). Bilateral prophylactic mastectomy is usually performed as a skin-sparing procedure with immediate reconstruction. Bilateral prophylactic mastectomy reduces breast cancer risk by more than 90 percent, but it is currently unclear whether overall or breast cancerâ€"specific survival is increased (Hartmann, 2001; Lostumbo, 2004; McDonnell, 2001; Peralta, 2000). Breast cancers may develop after prophylactic mastectomy if there is residual breast tissue (usually in the upper outer quadrant or axillary tail). They may also develop in the skin of a mastectomy flap.

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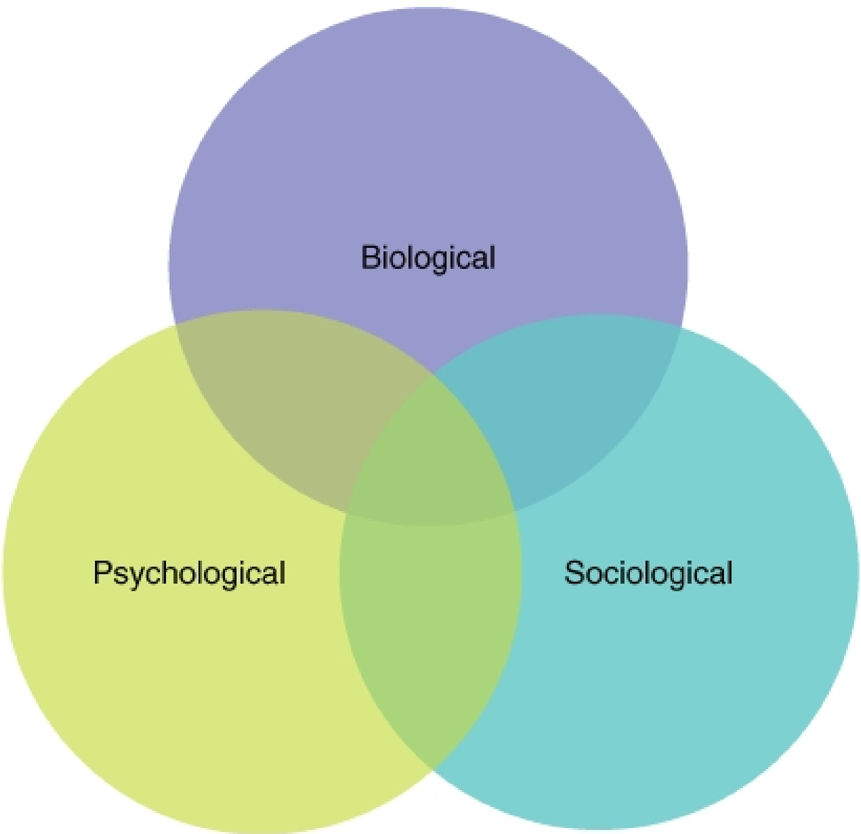
PSYCHOSOCIAL ISSUES AND FEMALE SEXUALITY: INTRODUCTION

Thirty years ago, an article in *Science* written by psychiatrist George Engel coined a word to describe a developing paradigm for patient care, the "biopsychosocial model" (Engel, 1977). The model encouraged formulating treatments that considered the mind and body of a patient as two intertwining systems influenced by yet a third systemâ€"society (Fig. 13-1). This was perhaps the first time a distinction was drawn between "disease" and "illness", the former referring to a pathologic process and the latter to the patient's experience of that process.

FIGURE 13-1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Biopsychosocial model. *(Redrawn from Engel, 1977, with permission.)*

Since the introduction of the biopsychosocial model, psychological factors have been found to play a dual role in their relationship with women's reproductive health. At times psychological factors are a consequence (infertility has been linked with psychological distress), and at other times are an insidious cause of a health problem (increased hysterectomies have been found in women with a low tolerance for the physical discomfort of menstruation) (O'Hara, 1995).

Twenty years before Engel introduced his paradigm for treatment, a German developmental psychologist, Erik Erikson (1963), created a model that describes psychological maturation across the life span. Combining these two models yields a dimensional perspective helpful for the evaluation, diagnosis, and treatment of any patient, and of particular relevance in a discussion of women's mental health (Table 13-1).

Table 13-1 Biopsychosocial Development

	Adolescence: 11â€“18 years	**Early Adulthood: 18â€“34 years**	**Middle Adulthood: 35â€“60 years**	**Late Adulthood: 61 yearsâ€“death**
Biologic	Pubertal hormonal changes Reproductive organ development Physical growth spurts Menarche Initiation of sexual activity	Hormonal activity Sexual activity Pregnancy	Hormonal changes Menopausal transition	Postmenopausal risks Age-related illness
Psychological	Identity construction Family functioning Peer relations Academic achievement	Role transitions Partner selection Motherhood Divorce Career choices and success Economic status	Marital status Late childbearing or "empty nest" Caring for aging parents Grandparenthood Career success and/or change Economic stability	Widowhood/divorce Remarriage Losses Retirement Extended family and friends Economic security
Social	School Home Neighborhood Church	College Workplace Home Neighborhood Church	Home Workplace Neighborhood Church Community	Home Neighborhood Church Community World-at-large

Not only do women use more health care services in general than men in the United States, but more women approach their physicians with psychiatric complaints, and more women have comorbid illness than men (Andrade, 2003; Burt, 2005; Kessler, 1994). Coupled with the almost universal recognition that primary care is where most patients with psychiatric illness are first seen, it is likely that obstetricians and gynecologists will often be the first to evaluate a woman in psychiatric distress (Goldberg, 2003). A clinical interview such as the one presented in Table 13-2 can guide assessment of a woman and includes all three domains from the biopsychosocial model.

Table 13-2 Psychiatric Assessment of Women: Clinically Significant Considerations	
Component	**Consideration**
History of present illness and past psychiatric history	Characterize symptoms in relation to: 1. A specific phase of the menstrual cycle 2. Use of hormonal contraception 3. Pregnancy 4. The postpartum period 5. Breast feeding or weaning 6. Abortion 7. Infertility treatment 8. Hysterectomy 9. Menopausal transition
Medications	Include exogenous hormones and all over-the-counter medications and supplements
Dietary assessment	Exclude ritualistic or restrictive eating patterns, binging, self-induced vomiting, and use of diet pills, laxatives, emetics, and diuretics
Alcohol and drug use	Exclude covert use, especially of prescription medications
Family psychiatric history	Include history of premenstrual dysphoric disorders and postpartum mood disorders
Medical history	Exclude autoimmune illnesses (e.g., lupus, thyroiditis, or fibromyalgia) that may present with psychiatric symptoms
	Exclude history of sexually transmitted disease that may affect current sexual functioning and childbearing capacity
Menstrual history	Exclude pregnancy, menstruation-related symptoms (e.g., bloating, weight gain, cramping, or breast tenderness)
	Exclude perimenopausal symptoms (e.g., irregular menstrual periods or hot flushes)
Social and developmental history	Note sexual preference, relationship styles, level of satisfaction with current relationships
	Document tendency to take on certain role relationships (e.g., caregiver, nurturer, or dependent or helpless role)
	Note current or past sexual, physical, or emotional abuse
Socioeconomic status	Note level of economic support and ability to meet ongoing financial needs
	If patient is a single mother, inquire about child support.

Adapted from Burt, 2005, with permission.

COMMON PSYCHIATRIC PRESENTATIONS

Mood, anxiety, and alcohol or substance use disorders are three families of psychiatric disorders commonly seen and often comorbid with reproductive disorders (American Psychiatric Association, 2000a). These three groups are defined by specific criteria described by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR), published by the American Psychiatric Association in 2000. Each family is characterized by a predominant feature, and each disorder within that family is identified by specific symptoms of that feature.

Mood Disorders

The spectrum of mood disorders is divided into depressive disorders (major depressive disorder, dysthymic disorder, and depressive disorder not otherwise specified); the bipolar disorders (bipolar I, bipolar II, cyclothymic disorder, and bipolar disorder not otherwise specified); and two etiologic disorders (mood disorder due to a general medical condition and substance-induced mood disorder) (Tables 13-3 and 13-4).

Table 13-3 Diagnostic Criteria for a Major Depressive Episode
A. ≥ 5 criteria present during the same 2-week period or a change from previous functioning At least one of these: Depressed mood most of the day, nearly every day (can be irritable in kids) Markedly diminished interest or pleasure in most activities, most of the day, most days
The balance of 5 from these: Significant weight loss/gain, change in appetite, or failure to make expected gains Insomnia or hypersomnia nearly every day Psychomotor agitation or retardation nearly every day, *observable by others* Fatigue or loss of energy nearly every day Feelings of worthlessness or excessive or inappropriate guilt nearly every day Diminished ability to think or concentrate or indecisiveness Recurrent thoughts of death, recurrent suicidal ideation, plans, or attempt
B. The symptoms do not meet the criteria for a Mixed Episode
C. Symptoms cause significant distress or impairment in functioning
D. Symptoms are not due to a substance or a general medical condition
E. Symptoms not better accounted for by bereavement ≥2 months or marked
Specifiers: Mild, Moderate, or Severe with or without Psychotic Features Chronic With Catatonic Features With Melancholic Features With Atypical Features With Postpartum Onset

Adapted from American Psychiatric Association, 2000a, with permisison.

Table 13-4 Diagnostic Criteria for Manic Episodes
Criteria for manic episodes
A. Distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week
B. During the period of mood disturbance, ≥3 of the following symptoms have persisted to a significant degree: Inflated self-esteem or grandiosity Decreased need for sleep More talkative than usual Flight of ideas or experiences racing thoughts Distractibility Increase in activity or psychomotor agitation Excessive involvement in pleasurable or risky activities with high potential for negative or painful consequences (e.g., promiscuity or unrestrained spending)
C. The criteria for a Major Depressive Episode are not fulfilled
D. The patient is markedly impaired occupationally or socially, is psychotic, or needs to be hospitalized to prevent harm to self or others
E. The symptoms are not due to the direct physiologic effects of a substance or a general medical condition
Criteria for a hypomanic episode
A. A distinct period of persistently elevated, expansive, or irritable mood, lasting throughout at least 4 days, that is clearly abnormal from the usual mood
B. During the period of mood disturbance, ≥ 3 of the above symptoms (same as for mania) have persisted to a significant degree
C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the person when not symptomatic
D. The disturbance in mood and the change in functioning are observable by others
E. The episode is not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization, and there are no psychotic features
F. The symptoms are not due to the direct physiologic effects of a substance or a general medical condition

Adapted from American Psychiatric Association, 2000a, with permission.

MOOD DISORDER PREVALENCE

The lifetime prevalence for mood disorders in the general U.S. population is approximately 20 percent (Kessler, 2005). Depression is the second leading cause for disability in women, and females are l.5 times more likely to suffer from a major depressive episode than men (National Institute of Mental Health, 2006). Women also commonly have one or more comorbid psychiatric disorders, most often anxiety disorder and/or substance use disorder.

DIAGNOSIS OF MOOD DISORDERS

Self-report questionnaires are often used to gauge the severity of depressive symptoms or identify individuals who require psychiatric evaluation. The Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) is one such tool that is easily implemented for clinical use (Tables 13-5 and 13-6) (Rush, 2003). By patient report, this questionnaire assesses symptom severity required by DSM-IV-TR criteria to diagnosis major depressive disorder. Further information about the instrument is available at www.ids-qids.org .

Table 13-5 The Quick Inventory of Depressive Symptomatology (16-Item) (Self-Report) (QIDS-SR_{16})

Name or ID: ______________________ Date: ______________________

CHECK THE ONE RESPONSE TO EACH ITEM THAT BEST DESCRIBES YOU FOR THE PAST SEVEN DAYS.

During the past seven days...

1. Falling Asleep:
- ☐ 0 I never take longer than 30 minutes to fall asleep.
- ☐ 1 I take at least 30 minutes to fall asleep, less than half the time.
- ☐ 2 I take at least 30 minutes to fall asleep, more than half the time.
- ☐ 3 I take more than 60 minutes to fall asleep, more than half the time.

2. Sleep During the Night
- ☐ 0 I do not wake up at night.
- ☐ 1 I have a restless, light sleep with a few brief awakenings each night.
- ☐ 2 I wake up at least once a night, but I go back to sleep easily.
- ☐ 3 I awaken more than once a night and stay awake for 20 minutes or more, more than half the time.

3. Waking Up Too Early:
- ☐ 0 Most of the time, I awaken no more than 30 minutes before I need to get up.
- ☐ 1 More than half the time, I awaken more than 30 minutes before I need to get up.
- ☐ 2 I almost always awaken at least one hour or so before I need to, but I go back to sleep eventually.
- ☐ 3 I awaken at least one hour before I need to, and can't go back to sleep.

4. Sleeping Too Much:
- ☐ 0 I sleep no longer than 7–8 hours/night, without napping during the day.
- ☐ 1 I sleep no longer than 10 hours in a 24-hour period including naps.
- ☐ 2 I sleep no longer than 12 hours in a 24-hour period including naps.
- ☐ 3 I sleep longer than 12 hours in a 24-hour period including naps.

During the past seven days...

5. Feeling Sad:
- ☐ 0 I do not feel sad.
- ☐ 1 I feel sad less than half the time.
- ☐ 2 I feel sad more than half the time.
- ☐ 3 I feel sad nearly all of the time.

Please complete either 6 or 7 (not both)

6. Decreased Appetite:
- ☐ 0 There is no change in my usual appetite.
- ☐ 1 I eat somewhat less often or lesser amounts of food than usual.
- ☐ 2 I eat much less than usual and only with personal effort.
- ☐ 3 I rarely eat within a 24-hour period, and only with extreme personal effort or when others persuade me to eat.

-OR-

7. Increased Appetite:
- ☐ 0 There is no change from my usual appetite.
- ☐ 1 I feel a need to eat more frequently than usual.
- ☐ 2 I regularly eat more often and/or greater amounts of food than usual.
- ☐ 3 I feel driven to overeat both at mealtime and between meals.

Please complete either 8 or 9 (not both)

8. Decreased Weight (Within the Last Two Weeks):
- ☐ 0 I have not had a change in my weight.
- ☐ 1 I feel as if I have had a slight weight loss.
- ☐ 2 I have lost 2 pounds or more.
- ☐ 3 I have lost 5 pounds or more.

-OR-

9. Increased Weight (Within the Last Two Weeks):
- ☐ 0 I have not had a change in my weight.
- ☐ 1 I feel as if I have had a slight weight gain.
- ☐ 2 I have gained 2 pounds or more.
- ☐ 3 I have gained 5 pounds or more.

During the past seven days...

10. Concentration / Decision Making:
- ☐ 0 There is no change in my usual capacity to concentrate or make decisions
- ☐ 1 I occasionally feel indecisive or find that my attention wanders.
- ☐ 2 Most of the time, I struggle to focus my attention or to make decisions
- ☐ 3 I cannot concentrate well enough to read or cannot make even minor decisions

11. View of Myself:
- ☐ 0 I see myself as equally worthwhile and deserving as other people
- ☐ 1 I am more self-blaming than usual.
- ☐ 2 I largely believe that I cause problems for others.
- ☐ 3 I think almost constantly about major and minor defects in myself.

12. Thoughts of Death or Suicide:
- ☐ 0 I do not think of suicide or death.
- ☐ 1 I feel that life is empty or wonder if it's worth living.
- ☐ 2 I think of suicide or death several times a week for several minutes.
- ☐ 3 I think of suicide or death several times a day in some detail, or I have made specific plans for suicide or have actually tried to take my life.

13. General Interest
- ☐ 0 There is no change from usual in how interested I am in other people or activities.
- ☐ 1 I notice that I am less interested in people or activities.
- ☐ 2 I find I have interest in only one or two of my formerly pursued activities.
- ☐ 3 I have virtually no interest in formerly pursued activities.

During the past seven days...

14. Energy Level:
- ☐ 0 There is no change in my usual level of energy.
- ☐ 1 I get tired more easily than usual.
- ☐ 2 I have to make a big effort to start or finish my usual daily activities (for example, shopping homework, cooking or going to work).
- ☐ 3 I really cannot carry out most of my usual daily activities because I just don't have the energy.

15. Feeling Slowed Down:
- ☐ 0 I think, speak, and move at my usual rate of speed.
- ☐ 1 I find that my thinking is slowed down or my voice sounds dull or flat.
- ☐ 2 It takes me several seconds to respond to most questions and I'm sure my thinking is slowed.
- ☐ 3 I am often unable to respond to questions without extreme effort.

16. Feeling Restless:
- ☐ 0 I do not feel restless.
- ☐ 1 I'm often fidgety, wringing my hands, or need to shift how I am sitting.
- ☐ 2 I have impulses to move about and am quite restless.
- ☐ 3 At times, I am unable to stay seated and need to pace around.

From Rush, 2003, with permission.

Table 13-6 Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR_{16}) Scoring Instructions

1. Enter the highest score on any one of the 4 sleep items (items 1 to 4)

   Enter the highest score on any one of the 4 weight items (items 6 to 9)

   Enter the highest score on either of the two psychomotor items (items 15 and 16)

2. There will be one score for each of the nine Major Depressive Disorder symptom domains
3. Add the scores of the 9 items (sleep, weight, psychomotor changes, depressed mood, decreased interest, fatigue, guilt, concentration, and suicidal ideation) to obtain the total score; total scores range from 0 to 27
4. 0â€“5: no depressive symptoms endorsed; 6â€“10: mild symptoms; 11â€“15: moderate symptoms; 16â€“20: severe symptoms; 21â€“27: very severe symptoms

From Rush, 2003, with permission.

Anxiety Disorders

Anxiety disorders have the highest prevalence rates in the U.S. Lifetime prevalence rates approximate 30 percent, and women are 1.6 times more likely to be diagnosed than men (Kessler, 2005). For women, the key transitions of menarche, pregnancy, and menopause may cause anxious feelings, because of the perceived irreversible life changes they may herald (see Chap. 21, Psychosocial Changes) (Bibring, 1959). Criteria established in the DSM-IV-TR may provide guidelines to help distinguish anxiety disorder from normally expected worries (Tables 13-7 and 13-8).

Table 13-7 Anxiety Disorders
Panic attack
Agoraphobia
Specific phobia
Social phobia
Obsessive-compulsive disorder
Posttraumatic stress disorder
Acute stress disorder
Generalized anxiety disorder
Anxiety disorder due to a general medical condition
Substance-induced anxiety disorder
Anxiety disorder not otherwise specified

Adapted from American Psychiatric Association, 2000a, with permission.

Table 13-8 Diagnostic Criteria for Generalized Anxiety Disorder
A. Excessive anxiety and worry occurring more days than not for at least 6 months, about a number of events or activities
B. The person finds it difficult to control the worry
C. The anxiety and worry are associated with three or more of the following six symptoms: 1. Restlessness or feeling keyed up or on edge 2. Being easily fatigued 3. Difficulty concentrating or mind going blank 4. Irritability 5. Muscle tension 6. Sleep disturbance
D. The focus of the anxiety and worry is not confined to features of another psychiatric disorder (e.g. worry about having a panic attack [Panic Disorder]; being embarrassed in public [Social Phobia]; gaining weight [Anorexia Nervosa])
E. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
F. The disturbance is not due to the direct physiologic effects of a substance or a general medical condition and does not occur exclusively during a Mood Disorder or a Psychotic Disorder

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Alcohol and Substance Disorders

In the United States, the lifetime prevalence of alcohol and substance disorders approximates 15 percent. This diagnosis is twice as likely in males, although rates in women are increasing (Kessler, 2005). Indicators of substance misuse are found in Tables 13-9 and 13-10. Often these disorders co-occur with depression and anxiety. In depth discussion of these issues is beyond the scope of this chapter, but additional information regarding alcohol and other commonly abused substances, including prescription medications, can be found at www.nida.nih.gov .

Table 13-9 Diagnostic Criteria for Substance Dependence
A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three or more of the following, occurring at any time in the same 12-month period:
(1) Tolerance, defined by either (a) a need for markedly increased amounts of the substance (b) markedly diminished effect with continued use of the same amount of the substance
(2) Withdrawal, manifested by (a) characteristic withdrawal syndrome for the substance (b) the same or a closely related substance is taken to relieve or avoid withdrawal symptoms
(3) The substance is often taken in larger amounts or over a longer period than is intended
(4) There is a persistent desire or unsuccessful efforts to cut down or control substance use
(5) A great deal of time is spent in activities necessary to obtain the substance, use the substance (visiting multiple doctors or driving long distances), or recover from its effects
(6) Important social, occupational, or recreational activities are given up or reduced because of substance use
(7) Substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance

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Table 13-10 Diagnostic Criteria for Substance Abuse
A. A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one or more of the following, occurring within a 12-month period (1) Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; neglect of children or household) (2) Recurrent substance use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by substance use) (3) Recurrent substance-related legal problems (e.g., arrests for substance-related disorderly conduct) (4) Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g., arguments with a spouse about the consequences of intoxication or getting into physical fights)
B. The symptoms have never met the criteria for Substance Dependence for this class of substance

Adapted from American Psychiatric Association, 2000a, with permission.

EATING DISORDERS

Eating disorders are classified by DSM-IV-TR as anorexia nervosa (AN), bulimia nervosa (BN), and eating disorder not otherwise specified (Tables 13-11 and 13-12). The core symptoms of both anorexia and bulimia are preoccupation with weight gain and excessive self-evaluation of weight and body shape. These disorders are 10 to 20 times more common in females than in males, particularly in those aged 15 to 24 years (Kaplan, 1998; Lucas, 1991). During adolescence, an estimated 4 percent of girls have some form of eating disorder, and approximately 0.3 percent suffers from anorexia nervosa. Anorexia usually begins early in adolescence and peaks around ages 17 to 18 years. Bulimia nervosa is more prevalent than anorexia but typically has a later onset (Hoek, 1998, 2006).

Table 13-11 Diagnostic Criteria for Anorexia Nervosa
A. Refusal to maintain body weight at or above a minimally normal weight for age and height (less than 85% of that expected)
B. Intense fear of gaining weight or becoming fat, even though underweight
C. Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low weight
D. In postmenarcheal females, amenorrhea
Restricting Type: No binge-eating or purging behaviors
Binge-Eating/Purging Type: Binge-eating and self-induced vomiting, or the misuse of laxatives, diuretics, or enemas

Adapted from American Psychiatric Association, 2000a, with permission.

Table 13-12 Diagnostic Criteria for Bulimia Nervosa
A. Recurrent episodes of binge eating 1. Eating, in a discrete period of time, an amount of food definitely larger than most people would eat in a similar period of time under similar circumstances 2. A sense of lack of control over eating during the episode
B. Recurrent inappropriate compensatory behavior to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, enemas, or other medications; fasting; or excessive exercise
C. Binge eating and inappropriate compensatory behaviors both occur, on average, at least twice a week for 3 months
D. Self-evaluation is unduly influenced by body shape and weight
E. The disturbance does not occur exclusively during episodes of Anorexia Nervosa
Purging Type: Regularly engaging in purging behaviors
Nonpurging Type: Compensatory behaviors are inappropriate, such as fasting or excessive exercise, but do not include vomiting or the misuse of laxatives

Adapted from American Psychiatric Association, 2000a, with permission.

Pathophysiology

The exact etiology of eating disorders is unknown. However, evidence suggests that there is a strong familial aggregation for eating disorders (Stein, 1999). In the restricting type of AN, the concordance rate among monozygotic twins has been shown to approximate 66 percent, and in dizygotic twins it is 10 percent (Treasure, 1989).

Various biologic factors have been implicated in the development of eating disorders. Abnormalities in neuropeptides, neurotransmitters, and the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal axes are reported (Stoving, 1999, 2001). In addition, psychological and psychodynamic factors related to an absence of autonomy are thought to influence obsessive preoccupations (Kaplan, 1998). Although eating disorders are believed to be a Western cultural phenomenon, rates of eating disorders are also increasing in nonwestern cultures (Fichter, 2004).

Diagnosis

ANOREXIA NERVOSA (AN)

This disorder is divided into two subtypes: (1) a restricting type and (2) a bulimic type, which is distinct from bulimia nervosa. Symptoms begin in the form of unique eating habits that become more and more restrictive. Advanced symptoms may include extreme food intake restriction and excessive exercise. Up to 50 percent of anorectics also show bulimic behavior, and these types may alternate during the course of anorexic illness. Bulimic-type anorectics have been found to engage in two distinct behavior patterns: those who binge and purge and those who solely purge.

Individuals with anorexia commonly defend their eating behaviors upon confrontation and rarely recognize their illness. They increasingly isolate themselves socially as their disorder progresses. Multiple somatic complaints such as gastrointestinal symptoms and cold intolerance are common. In the disorder's later stages, weight loss becomes more apparent and medical complications may prompt patients to seek help. These individuals often present with dental problems, general nutritional deficiency, electrolyte abnormalities (hypokalemia and alkalosis), and decreased thyroid function. Electrocardiogram changes such QT prolongation (bradycardia) and inversion or flattened T waves may be noted. Rare complications include gastric dilation, arrhythmias, seizure, and death.

BULIMIA NERVOSA (BN)

This disorder is identified by periods of uncontrolled eating of high-calorie foods (binges), followed by self-induced vomiting (purging). Moreover, bulimic women may often misuse laxatives or diuretics. Unlike anorexia, those with bulimia often recognize their maladaptive behaviors.

Most bulimics have normal weights, although their weight may fluctuate. Thus, physical findings may be more subtle. One of the most characteristic signs is knuckle calluses found on the dorsum of the dominant hand. Termed *Russell sign,* calluses form in response to repetitive contact with upper teeth and acidic stomach contents during purging (Strumia, 2005).

Comorbidity of Eating Disorders

Anorexia nervosa and bulimia nervosa are complex disorders, affecting both psychological and physical systems. These eating disorders often are accompanied by comorbid depression and anxiety symptoms. Rates of mood symptoms approximate 50 percent, and anxiety symptoms 60 percent (Braun, 1994). Simple phobia and obsessive-compulsive behaviors may also coexist. In many cases, patients with anorexia appear to have rigid, perfectionistic personalities and have low sexual interest. Patients with bulimia often display sexual conflicts, problems with intimacy, and impulsive suicidal tendencies (American Psychiatric Association, 2000b).

Prognosis of Eating Disorders

There are limited data concerning the long-term physical and psychological prognosis of women with eating disorders. Most may symptomatically improve with aging. However, complete recovery from anorexia nervosa is rare, and many continue to have distorted body perceptions and peculiar eating habits. Overall, the prognosis for bulimia is better than for anorexia.

Treatment of Eating Disorders

Treatment of eating disorders involves a multidisciplinary approach. The American Psychiatric Association practice guidelines for eating disorders include: (1) nutritional rehabilitation, (2) psychosocial treatment that includes individual and family therapies, and (3) pharmacotherapeutic treatment of concurrent psychiatric symptoms (American Psychiatric Association, 2000b). An online resource for information and support is provided by the National Eating Disorder Association, www.edap.org . However, health care providers should also be aware of proâ€"eating disorders websites, which may enable anorexic behaviors (Norris, 2006).

PREMENSTRUAL DISORDERS

Frequently, women of reproductive age experience symptoms during the late luteal phase of their menstrual cycle, and collectively these complaints are termed *premenstrual syndrome* (PMS) or *premenstrual tension* (PMT). Nearly 300 different symptoms have been reported and typically include both psychiatric and physical complaints (Table 13-13) (Halbreich, 2003a). For most women, these symptoms are self-limited. However, approximately 15 percent report moderate to severe symptoms that cause some impairment or require special consideration (Wittchen, 2002).

Table 13-13 Endicott Daily Record of Problem Severity

DAILY RECORD OF SEVERITY OF PROBLEMS

Please print and use as many sheets as you need for at least two FULL months of ratings.

Name or Initials ______________________

Month/Year ______________________

Each evening note the degree to which you experienced each of the problems listed below. Put an "x" in the box which corresponds to the severity: 1 - not at all, 2 - minimal, 3 - mild, 4 - moderate, 5 - severe, 6 - extreme.

Enter day (Monday="M", Thursday="R", etc) >																																
Note spotting by entering "S" >																																
Note menses by entering "M" >																																
Begin rating on correct calendar day >		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
1 Felt depressed, sad, "down,", or "blue" or felt hopeless; or felt worthless or guilty	6 5 4 3 2 1																															
2 Felt anxious, tense, "keyed up" or "on edge"	6 5 4 3 2 1																															
3 Had mood swings (i.e., suddenly feeling sad or tearful) or was sensitive to rejection or feelings were easily hurt	6 5 4 3 2 1																															
4 Felt angry, or irritable	6 5 4 3 2 1																															
5 Had less interest in usual activities (work, school, friends, hobbies)	6 5 4 3 2 1																															
6 Had difficulty concentrating	6 5 4 3 2 1																															
7 Felt lethargic, tired, or fatigued; or had lack of energy	6 5 4 3 2 1																															
8 Had increased appetite or overate; or had cravings for specific foods	6 5 4 3 2 1																															
9 Slept more, took naps, found it hard to get up when intended; or had trouble getting to sleep or staying asleep	6 5 4 3 2 1																															
10 Felt overwhelmed or unable to cope; or felt out of control	6 5 4 3 2 1																															
11 Had breast tenderness, breast swelling, bloated sensation, weight gain, headache, joint or muscle pain, or other physical symptoms	6 5 4 3 2 1																															
At work, school, home, or in daily routine, at least one of the problems noted above caused reduction of productivity or inefficiency	6 5 4 3 2 1																															
At least one of the problems noted above caused avoidance of or less participation in hobbies or social activities	6 5 4 3 2 1																															
At least one of the problems noted above interfered with relationships with others	6 5 4 3 2 1																															

From Endicott, 2006, with permission.

Premenstrual dysphoric disorder (PMDD) and *premenstrual dysphoria* (PMD) are independent clinical conditions that are identified

by an accompanying psychosocial or functional impairment. The degree of impairment is often equivalent to that seen in patients with minor depression or dysthymia (Halbreich, 2003b). Premenstrual dysphoric disorder carries significant functional impairment. Therefore, this diagnosis should be reserved for those who meet the strict DSM-IV-TR criteria (American Psychiatric Association, 2000a). In practice, however, the diagnosis of PMDD is often confused with PMD, particularly if a woman's complaints match some PMDD criteria. The prevalence of true PMDD in the general female population is thought to be 3 to 8 percent (Wittchen, 2002).

Pathophysiology of Premenstrual Syndrome

The exact causes of premenstrual disorders are unknown, although several different biologic factors have been suggested. Of these, estrogen and progesterone, as well as the neurotransmitters, γ-amino butyric acid (GABA) and serotonin, are frequently studied (Halbreich, 2003b).

SEX STEROIDS

Premenstrual syndrome is cyclic. Symptoms begin following ovulation and resolve with menses. They are less common in women with surgical oophorectomy or drug-induced ovarian hypofunction such as with gonadotropin-releasing hormone (GnRH) agonists. Moreover, women with anovulatory cycles rarely report PMS symptoms. For these reasons, research of PMS pathophysiology has focused on the sex steroids, estrogen and progesterone.

Central Nervous System Interaction

Estrogen and progesterone are neuroactive steroids and influence the central nervous system (CNS) neurotransmitters: serotonin, noradrenaline, and GABA. The predominant action of estrogen is neuronal excitability, whereas progestins are inhibitory (Halbreich, 2003b).

Specifically, premenstrual syndrome is believed to be in part associated with neuroactive progesterone metabolites. Of these, allopregnanolone is a potent modulator of GABA receptors, and its effects mirror those of low-dose benzodiazepines, barbiturates, and alcohol. These effects may include loss of impulse control, negative mood, and aggression or irritability (Backstrom, 2003). Wang and colleagues (1996) noted fluctuations in serum allopregnanolone across the various menstrual cycle phases. These changes were implicated with PMS symptom severity. However, this finding has not been consistently replicated by others (Rapkin, 1997; Schmidt, 1994; Sundstrom, 1998). Moreover, the significance of serum level changes relative to brain concentrations changes remains unclear.

SEROTONIN

Evidence also supports a role for serotonergic system dysregulation in the pathophysiology of PMS. Decreased serotonergic activity has been noted in the luteal phase. Moreover, trials of serotonergic treatments have shown symptom reduction in women with PMS (Cohen, 2004; Halbreich 2002a; Yonkers, 1996).

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

Sex steroids also interact with the renin-angiotensin-aldosterone system (RAAS) to alter electrolyte and fluid balance. The anti-mineralocorticoid properties of progesterone and possible estrogen activation of the RAAS system may explain PMS symptoms of bloating and weight gain.

Diagnosis of Premenstrual Syndrome

Women with PMS usually present with complaints from multiple systems, and these symptoms display temporal association with the menstrual cycle luteal phase. Symptoms must begin at least 5 days (American College of Obstetricians and Gynecologists [ACOG] criteria) or 1 week (DSM-IV-TR) before menses, and remit within 4 days (ACOG criteria) or a few days (DSM-IV-TR) after menses onset (American College of Obstetricians and Gynecologists, 2000). Evaluation of women complaining of PMS symptoms includes prospective daily symptom rating for at least two or three menstrual cycles. However, Borenstein and associates (2007) found that results from the Daily Record of Severity of Symptoms (Table 13-13) obtained on the first day of menses could be used for initial screening.

In certain instances, PMS symptoms may be an exacerbation of underlying primary psychiatric condition(s). Thus, during

evaluation, other common psychiatric conditions such as depression, dysthymia, and anxiety disorders should be excluded. Additionally, other medical conditions that have a multisystem presentation should be considered. These include hypothyroidism, systemic lupus erythematosus, endometriosis, anemia, fibromyalgia, chronic fatigue syndrome, fibrocystic breast disease, irritable bowel syndrome, and migraine.

Treatment of Premenstrual Syndrome

Commonly used treatments for PMS have focused on either symptom reduction or modification of underlying hormonal dysregulation. Clinicians may consider treatment options for mild to moderate cases. However, if treatment fails or if symptoms are severe, then psychiatric referral may be indicated.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Most psychotropic medications are effective in reducing psychological symptom severity. Several well-controlled trials of selective serotonin reuptake inhibitors (SSRIs) have shown these drugs to be efficacious and well tolerated (Cohen, 2002; Halbreich 2002b; Yonkers, 1996, 1997). Standard dosages of SSRIs with either an intermittent or continuous dosing strategy are now considered primary therapy for psychological symptoms of PMS (Table 13-14). In addition, short-term use of anxiolytics such as alprazolam or buspirone offer added benefits to some women with prominent anxiety. However, in prescribing anxiolytics, caution should be taken in women with prior history of substance abuse.

Table 13-14 List of Common Psychotropic Medications

Drug Class	Indication	Examples	Brand Name	Commonly Reported Side Effects	Pregnancy Category
Selective serotonin reuptake inhibitors (SSRIs)	Depressive, anxiety, and premenstrual disorders	Fluoxetine Citalopram Escitalopram Sertraline Paroxetine Fluvoxamine	Prozac, Sarafem Celexa Lexapro Zoloft Paxil Luvox	Nausea, headache, insomnia, diarrhea, dry mouth, sexual dysfunction	Class C, Paroxetine is Class D
Serotonin noradrenergic reuptake inhibitors (SNRIs)	Depressive, anxiety, and premenstrual disorders	Bupropion SR, XL Venlafaxine XR Duloxetine	Wellbutrin Effexor Cymbalta	Dry mouth, anxiety, agitation, dizziness, somnolence, constipation	Class C
Tricyclic and tetracyclic antidepressants	Depressive and anxiety disorders	Desipramine Nortriptyline Amitriptyline Doxepin Maprotiline	Norpramin Pamelor, Aventyl Elavil Sinequan Ludiomil	Drowsiness, dry mouth, dizziness, blurred vision, confusion, constipation, urinary retention and frequency	Class C, except maprotiline Class B and nortriptyline Class D

Benzodiazepines	Anxiety disorders	Alprazolam Clonazepam Diazepam	Xanax Klonopin Valium	Drowsiness, ataxia, sleep changes, impaired memory, hypotension	Class D
Others	Depressive and anxiety disorders	Nefazodone Trazodone	Serzone Desyrel	Headache, dry mouth, orthostatic hypotension, somnolence	Class C
	Anxiety disorders	Buspirone Hydroxyzine	Buspar Vistaril, Atarax	Dizziness, drowsiness, headache	Buspirone Class B, Hydroxyzine Class C
	Sleep agents	Zaleplon Zolpidem Ramelteon	Sonata Ambien Rozerem	Headache, somnolence, amnesia, fatigue	Class C

SR = sustained release; XR/XL = extended release.

ESTROGEN AND PROGESTERONE

Because gonadal hormonal dysregulation is implicated in the genesis of PMS symptoms, both estrogen and progesterone therapies have been evaluated. However, efficacy is highly variable with progesterone and to some extent with estrogen. Ford and colleagues (2006) reviewed randomized controlled studies that assessed progesterone treatment efficacy for PMS. They found "only a little good evidence" for progesterone use in treating premenstrual syndrome. Other studies evaluating estrogen, progesterone, and progesterone-blocking agent administration during the luteal phase have reported worsening patient PMS symptoms (Schmidt, 1998). Thus, due to the heterogeneous actions of estrogen and progesterone in PMS, it is difficult to predict who would likely benefit from exogenous treatment with these hormones.

In addition, data are limited in support of combination oral contraceptive (COC) pills for this indication. However, a unique COC, containing the spironolactone-like progestin drospirenone, (Yasmin, Berlex, Montville, NJ) shows preliminary evidence of therapeutic benefits for PMS symptoms (Freeman, 2001). Larger studies, however, are needed to confirm these findings.

OTHER AGENTS

Prostaglandin inhibitors offer benefits through their anti- inflammatory effects. Agents such as ibuprofen and naproxen sodium are commonly used for cramping and headaches associated with PMS (see Table 10-2). In addition, diuretics may be prescribed to alleviate fluid retention and leg edema. Spironolactone and dyazide (combined hydrochlorothiazide and triamterene) are commonly used agents. However, potential side effects are orthostatic hypotension and hypokalemia.

Gonadotropin-releasing hormone agonists and synthetic androgens such as danazol alleviate symptoms by suppressing ovulation. However, the poor tolerability of these therapies are weighed against the potential benefits in women with premenstrual disorders (see Chap. 9, GnRH Agonists).

Diet can aggravate PMS and foods and beverages high in sugar and caffeine may worsen symptoms (Johnson, 1995). In contrast, vitamins such as pyridoxine (vitamin B_6) and vitamin E may offer benefits. Pyridoxine is a cofactor to tryptophan hydroxylase, which is the key enzyme in serotonin synthesis (Wyatt, 1999). The recommended dose of pyridoxine is 50 to 100 mg/d orally, but doses exceeding 100 mg/d should be avoided to prevent pyridoxine toxicity. In smaller trials, minerals such as calcium and magnesium have shown benefits. Magnesium in combination with vitamin B_6 appears to reduce anxiety-related premenstrual symptoms (De Souza, 2000). Calcium benefits are possibly through calcium deficiencyâ€"related symptoms such as muscle cramps (Thys-Jacobs, 2000).

PREGNANCY AND POSTPARTUM DISORDERS

During pregnancy and the postpartum period, changing hormone levels, physical alterations, fatigue, and new social responsibilities often lead to psychological stress. Although pregnancy was previously viewed as protective against depression, some women experience the first onset of depression or other psychiatric disorders during this time. Moreover, pregnancy has been associated with relapse in psychotic disorders, and women with a history of depression are at the highest risk for suffering an episode during pregnancy or the postpartum period (Cohen, 2006a; O'Hara, 1996). Accordingly, clinicians should inquire specifically about any history of psychiatric distress, as this is the dominant risk factor for any psychiatric disorder during the perinatal period.

For the most part, psychiatric disorders during pregnancy have a course or presentation similar to those same disorders in nonpregnant women. For this reason, diagnostic criteria for psychiatric disorders do not change, but often the specifier "postpartum onset" is included in the diagnosis.

Mood Disorders in the Perinatal Period

DEPRESSION DURING PREGNANCY

Risks for Depression in Pregnancy

The prevalence of depression during pregnancy has been estimated to be highest (11 percent) in the first trimester, falling to 8.5 percent in the second and third trimesters. Most investigations of risk factors and predictors have been directed toward postpartum depression. However, a few studies have found that depression during pregnancy is often associated with adverse life events, chronic stress, limited social support, and past or current sexual or physical abuse (O'Hara, 1996).

Diagnosis of Depression in the Perinatal Period

The Edinburgh Postnatal Depression Scale (EPDS) is a screening measure specifically developed to screen for and assess severity of depressive symptoms during pregnancy and the postpartum (Cox, 1987). Unlike other depression screens that include symptoms that are also characteristic of pregnancy itself (appetite, weight change, sleep disturbance, and fatigue), this scale concentrates on the neurovegetative symptoms that are more descriptive of depression. Available in a number of languages, the EPDS is an efficient way for a clinician to identify patients that are at risk for being depressed both during pregnancy and postpartum. It is available through the American Academy of Pediatrics at: http://www.dbpeds.org/media/edinburghscale.pdf .

Treatment of Depression in Pregnancy

No antidepressant has been approved by the U.S. Food and Drug Administration (FDA) during pregnancy (Kornstein, 2001). However, SSRIs are commonly used antidepressants, and the FDA describes them as category C drugs except for paroxetine (Paxil, GlaxoSmithKline, Philadelphia, PA), which is category D (see Table 13-14). Recent evidence has caused concern regarding the safe use of SSRIs during pregnancy. In July 2006, the FDA issued a Public Health Advisory recommending a careful risk assessment during pregnancy. These drugs have been linked to persistent pulmonary hypertension in the newborn (PPHN). In addition, in 2005, the FDA issued a Public Health Advisory stating that paroxetine may increase the risk of congenital cardiac malformations.

However, women who discontinue antidepressant medication during pregnancy relapse into depression significantly more frequently than women who maintain their pharmacologic treatment (Cohen, 2006b). In addition, suicide remains a significant proportion of pregnancy-associated deaths (Shadigian, 2005). Thus, a clinician must assess the risk of relapse in a severely depressed women against potential risk to the newborn (Wisner 2000).

Nonpharmacologic approaches have also been used as potential treatment options during pregnancy. These include acupuncture, sleep cycle manipulation, cognitive-behavioral therapy, and interpersonal psychotherapy (Carter, 2004; Manber, 2004; Parry, 2000; Spinelli, 2003).

DEPRESSION IN THE POSTPARTUM

Risks

Depression after childbirth has largely been divided into three categories: "postpartum blues", postpartum depression, and

postpartum psychosis. The strongest predictors of postpartum depression include prior psychopathology, poor marital relationship, low levels of social support, and stressful life events in the previous 12 months (O'Hara, 1996).

CLASSIFICATION

Postpartum Blues

This transient state of heightened emotional reactivity can develop in up to 50 percent of women. The onset is 2 to 14 days after childbirth, and its duration is less than 2 weeks (Gaynes, 2005). Blues generally require no intervention. Rest and social support contribute significantly to remission. However, postpartum blues do constitute a significant risk factor for subsequent depression during the postpartum.

Postpartum Depression

According to the DSM-IV-TR, postpartum depression refers to the diagnosis of major depressive disorder within 4 weeks after childbirth. However, in research and most clinical settings, any depression developing within 12 months following childbirth is considered to have postpartum onset. With this definition, the prevalence of postpartum depression approximates 15 percent in postpartum women (Gaynes, 2005).

Postpartum depression warrants careful assessment by a mental health professional, as treatment should be initiated immediately to minimize impaired caregiving. Infants of depressed mothers have exhibited cognitive, temperamental, and developmental differences from infants of nondepressed mothers (Dawson, 1992; Murray, 1992; Whiffen, 1989). Selective serotonin reuptake inhibitors are usually first-line agents, although caution is necessary in breast feeding mothers. In addition, a number of psychosocial interventions have demonstrated efficacy in treating postpartum depression. Of these, the most significant effects have been achieved with cognitive-behavioral therapy and group therapy (Bledsoe, 2006; Boath, 2001). Additionally, Postpartum Support International is an excellent resource for information for both clinicians and patients. Information can be obtained at www.postpartum.net .

Postpartum Psychosis

This condition develops in less than 2 percent of new mothers, and its onset is generally within 2 weeks of childbirth (Gaynes, 2005). The risk for this severe form of depression is increased for women who have had prior mood disorders. Particularly, prior postpartum psychosis increases by 30 to 50 percent a woman's risk with subsequent deliveries (American Psychiatric Association, 2000a). Evaluation and antipsychotic pharmacologic treatment is essential for these women. Hospitalization is often indicated until the safety of mother and infant is assured.

Other Psychiatric Disorders in the Perinatal Period

Clinicians most often focus on mood disorders during the perinatal period. However, other psychiatric illnesses such as anxiety disorders, bipolar disorders, and schizophrenia may also present.

Of these, bipolar disorders and schizophrenia are serious, recurrent psychiatric illnesses that require pharmacologic treatment. Treatment planning is critical with such patients, and decisions should always be made in collaboration with a psychiatric professional. A careful balance must be struck between minimizing medication risk to the fetus and maternal risk from untreated or undertreated disease.

Perinatal Loss

Perinatal loss did not become a subject of professional research until the 1970s. Although many studies have focused on identifying factors that modify grieving styles, a few have focused on interventions with families after perinatal loss. Study results showed that health care providers were most helpful if they spoke directly, used understandable language, and shared information that would provide parents a sense of control over their situation and would address their fears. Additional time with health professionals and a perception of being a priority was also important to parents (DiMarco, 2001).

Since grief is individual, no generalizations can be made concerning patient support in such situations. Thus, a clinician must ask a patient what she needs and wants. Couples therapy may be helpful if mother and father find it difficult to grieve congruently.

Family therapy may be indicated if other children need support to process the loss and their parents' grief. Many hospitals provide support groups, and several on-line resources are available. Specifically, the Hygeia Foundation (www.hygeia.org) and the National Perinatal Association websites (www.nationalperinatal.org) offer helpful resources.

MENOPAUSAL TRANSITION AND MENOPAUSE

Risks for Psychiatric Disorders during Menopausal Transition

Menopausal transition has long been investigated as a vulnerable period for emergence of mood symptoms. Anxiety, irritable mood, and sleep problems are more likely to develop in perimenopausal women than in premenopausal women (Bromberger, 2001; Freeman, 2006). Moreover, recent data suggest that rates of new-onset depression during menopausal transition are nearly twofold greater than premenopausal rates (Cohen, 2006a). This risk persists even after adjusting for sleep disturbances and vasomotor symptoms.

Other possible risks for depression and anxiety are a prior history of depression, severe premenstrual distress, presence of hot flashes, and disrupted sleep. Demographic predictors of increased risk during the menopausal period are lower educational status, African-American ethnicity, unemployment, and major life stressors (Bromberger, 2001; Freeman, 2006; Maartens, 2002). Moreover, psychosocial issues include a woman's recognition that her reproductive years are ending and that her children will leave to establish their own lives. Developmentally, many women are transitioning from being focused on family to finding other avenues to invest time and energy.

Mood vulnerability during menopausal transition is believed to follow erratic physiologic fluctuations in reproductive hormones. A fuller discussion of these hormones as they relate to mood changes during this transition is found in Chapter 21, Psychosocial Changes.

Evaluation during Menopausal Transition

Women with psychological complaints warrant a comprehensive psychosocial inventory and risk factor assessment. Importantly, medical conditions may concurrently develop during this transition, may create psychological symptoms, and should be excluded. Specifically, thyroid function should be evaluated.

Treatment of Mood Symptoms during Menopausal Transition

The approach to treating mood symptoms involves both pharmacotherapy and psychotherapy. Recommended psychotropic medications are selective serotonin reuptake inhibitors and selective noradrenergic reuptake inhibitors (e.g., venlafaxine [Effexor, Wyeth, Madison, NJ]). These agents are good options for women who do not wish to take hormone therapy. Additional benefits include alleviation of vasomotor symptoms and improved sleep.

Studies suggest that short-term administration of estrogen is an option for perimenopausal women with depressive symptoms (Soares, 2001). However, this benefit should be weighed against safety concerns raised in the Women's Health Initiative (WHI) Study (see Chap. 22). The psychotropic role of estrogen-progesterone preparation in postmenopausal women remains unclear.

LATE LIFE

According to estimates by the U.S. Census Bureau, the number of older Americans will significantly increase over the next decade as the "Baby Boomer" generation ages. By 2030, nearly 20 percent of the population will be older than 65 years (He, 2005). Psychosocial issues addressed are significantly different for these women. Stressors may include diminished mental and physical function as well as loss of partner, family, or friends. Erikson identified the task of this final developmental stage of life as one of consolidation and integration. In this model, women retrospectively examine their lives. They may manage their last years with integrity and with satisfaction in a life well lived, or may suffer despair, feeling that all was in vain.

Mental Disorders in the Elderly

According to the 2000 U.S. census, functionally impairing mental disorders affected 11 percent of adults aged 65 to 74 and 10 percent of those older than 74 (He, 2005). Of these disorders, depression, anxiety, late-onset psychotic and paranoid disorders, and alcoholism are those most likely to be observed in a clinical practice (Zarit, 1998). However, the prevalence of depression is generally thought to be lower in postmenopausal women compared with reproductive-aged women. Moreover, most studies suggest that the gender gap between rates of depression closes in late life. As in the general population, anxiety is the most common psychiatric disorder in the elderly (Zarit, 1998).

Evaluation of Psychiatric Disorders in Late Life

If a psychiatric disorder is suspected, careful evaluation is required to exclude underlying medical causes for these changes. For example, depression may be a comorbid disorder with or an early symptom of Alzheimer and Parkinson disease (Polidori, 2001). Alternatively, depression, anxiety, and psychosis may also result from single medications or medication combinations.

Specific screening questionnaires for depression have been developed for the elderly, such as the Geriatric Depression Scale (Brink, 1982). This screening tool is available in various languages at: http://www.stanford.edu/~yesavage/GDS.html . In addition, neuropsychological evaluation is helpful to discriminate between the source and nature of mood symptoms and cognitive impairment.

Treatment of Psychiatric Disorders in Late Life

Recognizing the natural decline in serotonin levels with aging, many gerontologists prescribe SSRIs for their patients. However, communication between all treating physicians to coordinate medications and minimize interactions is particularly important for elderly patients.

Psychosocial treatments are often helpful for the patient and, where applicable, her caregivers. Cognitive-behavioral therapy and interpersonal therapy have both been found efficacious with the elderly. Moreover, family therapy can be of great value to those struggling with end-of-life issues, functional impairments, multiple losses, and caregiver burden. Social workers are also of tremendous value if a patient and family need to locate additional resources for care.

A meta-analysis of 89 treatment studies found that pharmacotherapy and psychotherapy achieved comparable results in treatment of depression. Thus, treatment planning may be individualized and should assess patient preference, contraindications, and treatment access (Pinquart, 2006).

ADDITIONAL DISORDERS THAT PRESENT ACROSS THE LIFE SPAN

Somatoform Disorders

Recurrent, multiple, often unexplained physical symptoms are hallmark features of somatoform disorders. These disorders are common, and their estimated prevalence in general clinical practice is 16 percent (de Waal, 2004). Their prevalence may be even higher in specialty clinics such as pain management clinics.

Somatoform disorders are complex and poorly understood. However, symptoms cause significant distress and/or impairment in various domains of an affected individual's life. Moreover, one in four somatoform patients suffer from comorbid anxiety and depressive symptoms. Thus, a multidisciplinary approach is often required to effectively manage these women's symptoms.

SEXUAL ASSAULT

Sexual assault is a crime of violence, often motivated by aggression and rage, with the assailant using sexual contact as a weapon for power and control. Sexual assault can include a range of coercive behaviors ranging from kissing, fondling, and molestation, to rape or attempted rape. Linden (1999) defines sexual assault as "an event that occurred without the victim's consent, involved the use of force or the threat of force, and involved actual or attempted penetration of the victim's vagina, mouth, or rectum".

According to recent statistics, one in eight women will be raped during her lifetime, and 39 percent will be sexually assaulted more than once (Kilpatrick, 1992). Many rapes are unreported, because of a victim's feelings of shame and guilt. Alternatively, a victim may not define the event as rape (e.g., spousal and date rape).

Well-known sequelae of rape include isolation, depression, anxiety, somatic symptoms, suicide attempts, and posttraumatic stress disorder (PTSD). The experience has a strong effect on the victim's subsequent health and thus is a major public health issue. Importantly, in caring for sexual assault victims, clinicians should be familiar with the complex array of reactions (emotional and physical), common injuries, and elements of proper evaluation and treatment of these patients.

Common Physical Findings with Sexual Assault

Initial evaluation of a sexual assault victim should concentrate on identifying serious injuries. Although 70 percent of rape victims sustain no obvious physical injuries, 24 percent sustain minor injuries, and up to 5 percent sustain major nongenital injuries. Although death is rare (0.1 percent sustain fatal injuries), the fear of death during an assault is one of the most intense reactions (Deming, 1983; Marchbanks, 1990). The most common nongenital injuries in sexual assault victims include bruises, cuts, scratches, and swelling (81 percent); internal injuries and unconsciousness (11 percent); and knife or gunshot wounds (2 percent) (Sommers, 2001). In the genital area, the posterior fourchette is the area most often injured.

Once life-threatening injuries are excluded, a woman should be moved to a quiet, private setting for further evaluation. A systematic, thorough, but compassionate approach to obtaining a history and collecting evidence is essential for appropriate treatment of the victim and for future prosecution of her assailant.

Rape Examination and Legal Documentation

Although valid evidence may be collected up to 5 days after sexual assault, immediate examination increases the opportunity to obtain valuable physical evidence (Table 13-15). Consent is obtained prior to physical and genital examination and evidence collection. This step helps to re-establish a victim's sense of control and is essential for entry of evidence in a court of law (Plaut, 2004). Providers should emphasize that vital information may be lost if evidence is not collected early, and that evidence collection does not commit a victim to pressing criminal charges (Linden, 1999). Moreover, a patient should be counseled that she may terminate an examination if it is too emotionally or physically painful.

Table 13-15 Important Elements of Physical Examination and Evidence Collection Following Sexual Assault
Physical examination
General appearance
Affect/emotional status
Complete examination of head, body, and extremities, with body diagram of injuries
Pelvic examination, with colposcopy if available to exclude lower reproductive tract trauma
Elements of evidence collection
Swabs and smears of involved orifices
Saliva sample from the patient
Fingernail scrapings from the patient, if the victim scratched the assailant's skin or clothing
Clothing collected in labeled paper bags
Head hair combings, head hairs cut or pulled from patient
Pubic hair combings, pubic hair cut or pulled from patient
Blood sample for patient blood typing

Most states have standardized kits for evidence collection and storage in which kits may be locked to ensure that legal evidence procedures are maintained. Documentation of all physical injuries is essential, and objective evidence of trauma (even minor) is associated with increased chances of successful prosecution. Clothing is collected as a patient undresses on a white sheet and placed in properly labeled bags. Any debris, such as hair, fibers, mud, or leaves should also be collected.

Evidence gathering includes a sample of the patient's saliva and swabs of all involved orifices. A thorough pelvic examination with evidence collection is essential, even if there are no complaints of genital pain. Up to one third of victims can have traumatic genital injuries without symptoms. Common patterns of genital injury include tears of the posterior fourchette and fossa, labial abrasions, and hymenal bruising. Significant genital injuries are more common in postmenopausal or prepubertal victims. Colposcopy should be used if available because this technique increases detection of more subtle injuries of the cervix and vagina. Lenahan (1998) reported that the use of colposcopy increased genital trauma recognition from 6 percent to 53 percent. In addition, a Wood lamp may aid identification of semen on the skin, which then should be collected with moistened cotton swabs. A blood sample is collected for typing, to differentiate the blood type of the victim from that of the assailant. After evidence is collected, it is signed, sealed, and locked in a secure place (Rambow, 1992).

Treatment Following Sexual Assault

PREGNANCY PREVENTION

Medication prophylaxis to prevent pregnancy and common sexually transmitted diseases is provided to women following sexual assault. The risk of rape-related pregnancy is estimated at 5 percent per rape among reproductive-aged victims (Holmes, 1996). Most of these pregnancies, unfortunately, occur in adolescents, who are often the victims of incest and who never report the incident or receive medical attention. Because of variation in a woman's menstrual cycle, pregnancy prophylaxis, also termed *emergency contraception,* should be offered to all victims (see Chap. 5, Emergency Contraception). Prophylaxis can be administered for up to 72 hours after rape, but is most effective in the first 24 hours (Table 13-16). In some studies, prophylaxis

was effective for up to 5 days following rape.

Table 13-16 Pregnancy and Sexually Transmitted Disease Prevention Following Sexual Assault
Testing
Pregnancy test (urine or serum)
Hepatitis antibodies
Venereal Disease Research Laboratory (VDRL) test (consider)
Cultures for Neisseria gonorrhoeae and Chlamydia trachomatis
Microscopic evaluation of vaginal discharge saline prep
Treatment
Plan B: levonorgestrel 0.75 mg, one pill orally every 12 hours for two doses
Ceftriaxone 125 mg intramuscularly, single dose
Azithromycin 1 g orally, single dose
Optional treatment
Hepatitis B vaccination (see Table 1-1).
Metronidazole 2 g orally, single dose
Human immunodeficiency virus prophylaxis with zidovudine, 200 mg orally three times daily and lamivudine, 150 mg orally twice daily for 4 weeks

A negative pregnancy test to exclude preexisting pregnancy should be confirmed before administering emergency contraceptive methods. Side effects of estrogen/progestin combinations include nausea (in up to 50 percent of patients), and vomiting (in up to 20 percent), breast tenderness, and heavier menstrual period. With use of Plan B (levonorgestrel 0.75 mg, one pill taken orally every 12 hours for two doses), the risk of nausea is reduced to 23 percent and vomiting to 6 percent (Arowojolu, 2002). An antiemetic can be prescribed one-half hour prior to administration to decrease nausea.

Patients should be informed that their next menses may be delayed following this prophylaxis. Although current regimens are 74 to 89 percent effective, women should be counseled to return if their next menses is more than 1 to 2 weeks late (Yuzpe, 1982; Trussell, 1996; Task Force on Postovulatory Methods of Fertility Regulation, 1998).

SEXUALLY TRANSMITTED DISEASE PREVENTION

The risk of acquiring a sexually transmitted disease (STD) after rape has been estimated. The risk of developing trichomoniasis is approximately 12 percent; bacterial vaginosis, 12 percent; gonorrhea, 4 to 12 percent; chlamydial infection, 2 to 14 percent; syphilis, 5 percent; and human immunodeficiency virus (HIV) infection, <0.1 percent (Jenny, 1990; Katz, 1997; Schwarcz, 1990). However, these risks are difficult to predict and vary by geographic location, type of assault, assailant, and presence of preexisting infections. General recommendations describe antibiotic prophylaxis for hepatitis, gonorrhea, and chlamydia (see Table 13-16).

The fear of contracting HIV after sexual assault is common in survivors and is often the primary concern after a rape (Baker, 1990). However, prophylaxis against HIV remains controversial, given the low risk of transmission following a single sexual assault (Gostin, 1994). Although the Centers for Disease Control and Prevention (CDC) has no formal recommendations for HIV prophylaxis in this setting, many experts recommend offering prophylaxis to candidates who are willing to take the full course of

medications and comply with surveillance testing. The risks and side effects of these medications and need for close monitoring should be discussed with patients (Katz, 1997, 1998).

PSYCHOLOGICAL RESPONSE TO SEXUAL ASSAULT

Survivors of sexual assault may display an array of reactions that commonly include anxiety, agitation, crying, or a quiet, calm, and detached affect. In 1974, Burgess and Holmstrom first characterized the "rape trauma syndrome". They described two response phases to the trauma of sexual assault: (1) the acute disorganization phase, lasting several weeks, and (2) the reorganization phase, lasting from several weeks to years. During the acute phase, common initial emotional reactions include shock and disbelief, fear, shame, self-blame, humiliation, anger, isolation, grief, and loss of control. Somatic reactions may be common. During the reorganization phase, feelings of vulnerability, despair, guilt, and shame may continue. Symptoms may include nonspecific anxiety, somatic complaints, or depression.

SUBSEQUENT CARE FOLLOWING SEXUAL ASSAULT

Survivors should be referred to local rape crisis centers and encouraged to visit within 1 to 2 days. All sexual assault victims should receive medical evaluation at 1 to 2 weeks, and 2 to 4 months following their rape. During these visits, examination for STDs and blood testing for HIV and syphilis (rapid plasma reagin [RPR]) should be performed. Remaining hepatitis vaccinations are administered, if needed (see Table 1-1).

DOMESTIC VIOLENCE

Defining Domestic Violence

The terms *domestic violence* (DV), *gender-based violence,* or *violence against women,* encompasse a multitude of abuses directed at women and girls. The United Nations Declaration on the Elimination of Violence Against Women (United Nations General Assembly, 1993) defines violence as acts that cause, or have the potential to cause harm. Introduction of the term "gender based" emphasizes that the act is rooted in inequality between women and men (Krantz, 2005). *Intimate partner violence* (IPV) refers to harm inflicted by one intimate partner on the other, with the intention of causing pain or controlling the other's behavior.

Violence against women varies and includes wife battering, rape, sexual assault, incest, and elder abuse (Burge, 1997; Straka, 2006). Most victims know their assailant and have been assaulted more than once. The average length of victimization is 4 years for repeatedly raped women and for physically assaulted women (Tjaden, 2000).

Domestic Violence Statistics

The CDC National Center for Injury Prevention and Control estimates that nearly 5.3 million incidents of intimate partner violence occur each year among U.S. women aged 18 years and older. These incidents result in nearly 2 million injuries and 1,300 deaths nationwide every year. Three studies conducted in family practice settings found that the lifetime prevalence of husband-to-wife violence (slapping or worse) ranged from 36 to 44 percent (Elliott, 1995; Hamberger, 1992; Pence, 1993).

Risk Factors Associated with Domestic Violence

YOUNG ADULTHOOD

Aside from youth, few traits characterize women who are assaulted by violent men. Peters and colleagues (2002) analyzed data from 5,298 domestic violence reports. They found that women aged 16 to 24 years are at greatest risk for DV, a risk that was more than twice as great as the risk for women aged 25 to 34 years. Rates of domestic violence decreased throughout women's reproductive years and reached a nadir in women aged 65 or older. Hotaling and Sugarman (1986) in their review found only one consistent risk marker of being an abused wife. Witnessing violence as a child was a significant risk factor in 11 of 15 studies.

DOMESTIC VIOLENCE DURING PREGNANCY

Women should be screened for domestic violence during the perinatal period. Seven to 20 percent of pregnant women may be victims, and homicide is reported as the leading cause of death during pregnancy. Most cases result from partner abuse (Gazmararian, 1996; Shadigian, 2005). Therefore, screening for interpersonal violence is an important component of prenatal care. The Antenatal Psychosocial Health Assessment (ALPHA) is a questionnaire that evaluates psychosocial health during pregnancy and

contains sections that screen for domestic violence. This screening tool can be found at: http://dfcm.utoronto.ca/research/alpha/pdf/en/alphaformlarge.pdf .

DOMESTIC VIOLENCE IN LATE LIFE

The social and medical problem of elder abuse is escalating with an increasingly elderly population. Currently, an estimated 2 million older adults are mistreated annually, and 84 percent of cases are unreported (Jayawardena, 2006). Elder abuse is divided into seven categories by The National Center on Elder Abuse: physical, emotional, and sexual abuse; financial exploitation, neglect; self-neglect; and miscellaneous (Tatara, 1997). Of these categories, neglect is the most prevalent form of mistreatment. It occurs most often in the home and is perpetrated most frequently by family members. Identified risk factors are caregiver stress, patient cognitive impairment and need for assistance with daily life activities, conflicted family relationships, and poor social support.

Diagnosis

Women who have been assaulted are far more likely to seek help from their medical provider than from legal personnel, mental health professionals, or victim advocates. Victims of violence have an unusually high rate of medical use for years after the assault and may present with psychiatric and somatic complaints to their primary care provider (Koss, 1992). Although some clinicians may feel awkward asking patients, researchers agree that *the single most important thing a physician can do for a battered woman is to ask about violence* (Linden, 1999). Additionally, health care providers should ask about violence if they identify symptoms or behaviors that may be associated with victimization (Burge, 1997). These may include bruising, unexplained injuries, depression or anxiety, alcohol or drug abuse, unexplained chronic pain, isolation, inability to cope, limited access to care, noncompliance, husbands with extremely controlling behaviors or intense jealousy, or husbands with substance abuse.

Management of Domestic Violence

PATIENT VALIDATION AND REFERRAL

If a patient discloses domestic violence, a clinician should validate and normalize a patient's perspective. Patients should be counseled that many women have assault experiences, that most are afraid to confide these, that memories about the experience can be painful, and that a fear of future assaults is a reasonable fear. Following disclosure, a clinician should express concern for the woman's health and safety and convey a willingness to discuss relationship issues at any time. Moreover, information describing community resources should be offered. The National Domestic Violence Hotline (1-800-799-SAFE [7233]) is a nonprofit telephone referral service, with access to more than 5,000 women's shelters nationally.

DOCUMENTATION

Battery is a crime, yet few states specifically require reporting of domestic violence. A small number of states require mandatory arrest of batterers, and a few jurisdictions aggressively pursue cases of domestic violence. Accordingly, each clinician should know their state laws to properly and adequately inform their patients. In addition, providers should thoroughly document physical findings of violence. Such data may be required if criminal charges are pursued.

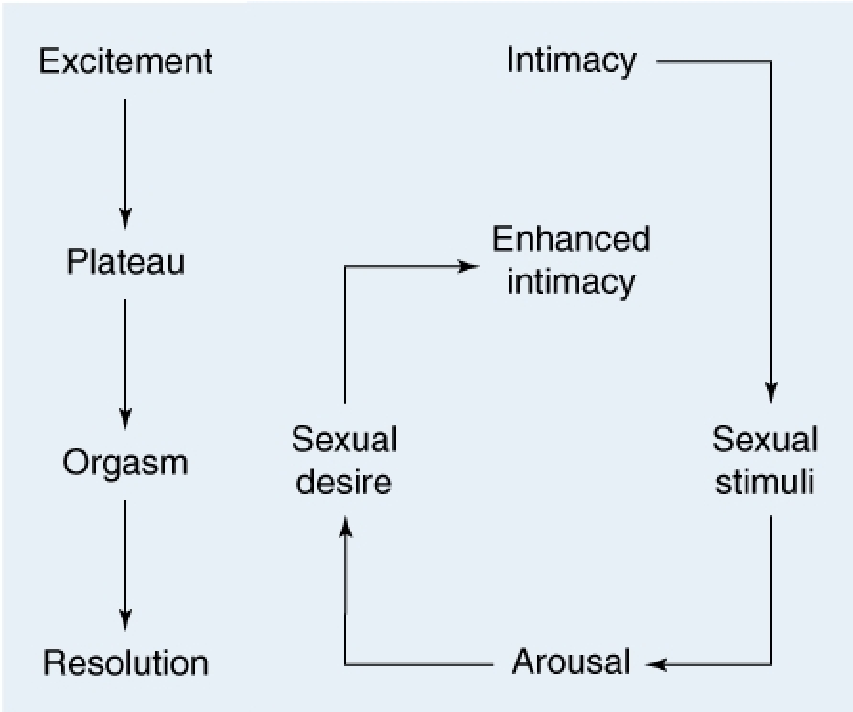
FEMALE SEXUALITY

Sexuality is one of the most complex and yet basic components of human behavior. Expressions of sexuality and intimacy remain important throughout the life span. Although basic sexual drive is biologic, its expression is determined by a variety of psychological, social, environmental, spiritual, and learned factors. Thus, sexual satisfaction is often less dependent on the physical components of sexuality than on the quality of the relationship and the context in which sexual behavior is undertaken.

Biologic Cycle

In describing the sexual response cycle, several investigators have assumed that sexual responses follow a predictable sequence of events. The number of stages within this response cycle varies, and cycles containing from two to four stages have been described (Fig. 13-2). Rather than the traditional view of the sexual response cycle progressing through discrete sequential stages of desire, arousal, orgasm, and resolution, it is now recognized that these phases overlap and that their sequence may vary (Basson, 2006).

FIGURE 13-2



Models of female sexual response. (*Adapted from Masters, 1966, and Basson, 2000, with permission.*)

Drive and Desire

The basis of desire and perceived arousal in women is poorly understood, but it appears to involve interactions among multiple neurotransmitters, sex hormones, and environmental factors. Early in the female sexual response cycle, erotic stimulation is associated with a desire, also termed *libido,* for sexual interaction. Libido varies and is considered to be the cerebral component of sexuality.

Several other factors have been closely linked to women's sexual satisfaction and libido. Based on survey data, these include stable past and current mental health, positive emotional well-being and self image, rewarding past sexual experiences, positive feelings for the partner, and positive expectations for the relationship (Bancroft, 2003; Dennerstein, 2005; Laumann, 2005).

Arousal

A woman's sexual arousal is complex and correlates positively with the sexual stimulus and its emotional context. This subconscious reflex is organized by the autonomic nervous system and processed in the limbic system in response to mental or physical stimuli that are recognized as sexual. Subjective findings of sexual arousal include vaginal and vulvar congestion, increases in vaginal lubrication, and other somatic changes such as blood pressure level, heart rate, muscle tone, respiratory rate, and temperature. However, investigators have found that in sexually healthy women, measurements of genital congestion and subjective arousal vary widely (Everaerd, 2000; Laan, 1995). There are also affective responses to sexual arousal. Feelings of joy and affirmation or feelings of fear, guilt, and awkwardness serve as cognitive feedback and modulate arousal.

CLITORAL CHANGES WITH AROUSAL

In the basal state, clitoral corporal and vaginal smooth muscles are tonically contracted. After sexual stimulation, neurogenic and endothelial release of nitric oxide (NO) leads to clitoral cavernosal artery relaxation. Arterial inflow follows, and creates increased clitoral intracavernosal pressure and clitoral engorgement (Cellek, 1998). Extrusion of the glans clitoris and enhanced sensitivity results.

VAGINAL AND VULVAR CHANGES WITH AROUSAL

In the basal state, the vaginal epithelium reabsorbs sodium from the submucosal capillary plasma transudate. However, after sexual stimulation, several neurotransmitters, including NO and vasoactive intestinal peptide (VIP), are released. These modulate vaginal vascular and nonvascular smooth muscle relaxation (Palle, 1990). Dramatic increases in submucosal capillary flow follow and overwhelm sodium reabsorption. Three to 5 mL of vaginal transudate is produced, and this enhanced lubrication is essential for pleasurable coitus. Vaginal smooth muscle relaxation increases vaginal length and luminal diameter, especially in the distal two thirds of the vagina.

Release

Masters and Johnson (1966) proposed that orgasmic release is a reflex-like response that follows once a plateau of excitement has been reached or exceeded. The physiologic and behavioral indices of orgasm involve the whole bodyâ€"facial grimaces, generalized myotonia of the muscles, carpopedal spasms, and contractions of the gluteal and abdominal muscles. For women, orgasm is also marked by rhythmic contractions of the uterus, the vaginal barrel, and the rectal sphincter, which gradually diminish in intensity, duration, and regularity following orgasm. The subjective experience of orgasm includes a feeling of intense pleasure with a peaking and rapid, exhilarating release. These sensations are reported to be singular, regardless of the manner in which orgasm is achieved (Newcomb, 1983). Women are unique in their ability to be multiorgasmic, that is, capable of a series of distinguishable orgasmic responses without a lowering of excitement between them.

Resolution

After orgasm, the anatomic and physiologic changes of excitement reverse. In women, genital vasocongestion diminishes, and the vagina shortens and narrows. A filmy sheet of perspiration covers the body, and elevated heart and respiration rates gradually return to normal. If orgasm has occurred, there is concomitant psychological and physical relaxation. If orgasm does not occur, a similar physiologic processes occurs, but at a slower rate.

Normal Variations in the Physiologic Response

Sexual function and variations in the physiologic response may be affected by many biologic and psychological aspects of reproduction and the life cycle.

PREGNANCY AND SEXUALITY

During pregnancy, sexual function may change, and a reduction in sexual desire and coital frequency is typical (Byrd, 1998). These changes may stem from fears of causing fetal harm during intercourse or orgasm. In addition, fatigue, physical discomfort, or feeling less physically attractive are other reasons.

Women who suffer recurrent miscarriage, infertility, or undergo therapeutic abortion and even those during a normal postpartum will have alterations in their physiologic and psychological sexual response. Byrd (1998) found that women who are breast feeding report less sexual activity and less satisfaction than those who were not breast feeding. The study failed to demonstrate any marked differences according to the method of delivery, although women who had cesarean delivery were more likely to resume intercourse 4 weeks postpartum than women who had delivered vaginally.

SEXUALITY DURING MENOPAUSAL TRANSITION

The baseline data from the Study of Women's Health Across the Nation (SWAN) addressed sexual behavior in 3,262 women aged 42 to 52 years who were either premenopausal or in early menopausal transition. Evidence suggests that in early menopausal transition, there were few changes in sexual practices or function (Cain, 2003)

Late in menopausal transition and with natural menopause, hormonal changes can interfere with physiologic response (Avis, 2000). Masters and Johnson (1966) described a delay in reaction time of the clitoris, delayed or absent vaginal lubrication, decreased vaginal congestion, and reduced duration of contractions with orgasm. Loss of estrogen diminishes genital blood flow, vaginal lubrication, and vaginal tissue structural integrity (Freedman, 2002; Pauls, 2005). Moreover, Sarrel (1990) correlated improved libido and orgasm with estrogen replacement in postmenopausal women. Others have shown improvement in vaginal lubrication, blood flow, and vaginal compliance in menopausal women taking systemic estrogen replacement, but these were not

correlated with subjective improvements in sexual function (Berman, 1999).

SEXUALITY IN LATE LIFE

With aging, sexuality still plays an important role in the maintenance of physical and mental health. Dennerstein (2001) suggests that even many years after menopause, an increase in desire and interest is consistently reported with a new relationship. The opportunity for sexual activity in the form of intercourse, however, is often dependent on partner issues. Both partner availability and partner health begin to shape the frequency with which this form of sexual activity occurs. Of older women, 40 to 47 percent masturbate.

In general, sexual activity declines with increasing age. Activity is reported in 30 to 78 percent of 60-year-old women, in 11 to 74 percent of those older than 70 years, and in 8 to 43 percent of 80-year-old women (Morley, 2003). Few data describe sexual function in those older than 80, but as the "Baby Boomer" cohort of a more sexually open group continues to age, the future holds promise for the desire to maintain this quality of life.

SEXUAL DISORDERS

Psychiatric sexual dysfunctions are characterized by painful intercourse or disturbances in desire, arousal, orgasm, or resolution that cause marked distress and relationship difficulty (Table 13-17). Sexual dysfunction stemming from dyspareunia may also originate from gynecologic disease and is discussed more fully in Chapters 4, Symptoms of Vulvodynia and 11, Dyspareunia.

Table 13-17 Sexual Function Disorders
Hypoactive sexual desire disorder
Persistently or recurrently deficient or absent sexual fantasies and desire for sexual activity, taking into account factors such as age and the context of the person's life
Sexual aversion disorder
Persistent or recurrent extreme aversion to and avoidance of all genital sexual conduct with a sexual partner
Female sexual arousal disorder
Persistent or recurrent inability to attain or maintain until completion of sexual activity an adequate lubrication-swelling response of sexual excitement
Dyspareunia
Recurrent or persistent genital pain associated with sexual intercourse (not caused exclusively by vaginismus or lack of lubrication)
Vaginismus
Recurrent or persistent involuntary spasm of the musculature of the lower third of the vagina that interferes with sexual intercourse
In all the above disorders
The disturbance causes marked distress or interpersonal difficulty
Sexual dysfunction is not better accounted for by another psychiatric disorder and is not due exclusively to the direct physiologic effects of a substance or a general medical condition
Types: Lifelong vs. acquired; generalized vs. situational; due to psychological factors vs. due to combined factors

Adapted from American Psychiatric Association, 2000a, with permission.

Incidence

Although many studies have investigated female sexual dysfunction, prevalence rates are difficult to establish due to differing criteria and measures of sexual functioning. However, a recent literature review estimated that 64 percent of women experience low or no sexual desire, 35 percent have difficulty achieving orgasm, and 26 percent experienced sexual pain (Hayes, 2006). Most difficulties last less than 6 months, but one third may persist longer.

Risk Factors

Psychosocial risk factors for sexual dysfunction include comorbid psychological disorders, negative emotions, maladaptive cognitions (such as inaccurate expectations), cultural factors, lack of education regarding sexual functioning, couple distress, and absent physical attraction. Of these, psychiatric disorders such as depression and anxiety are frequently comorbid with sexual disorders. Thus, for most patients who suffer from sexual dysfunction, evaluations should not stop with an organic explanation (Bach, 2001).

Evaluation of Sexual Dysfunction

In accordance with the biopsychosocial approach, diagnosis of sexual disorders begins by judging if dysfunction is caused exclusively by a general medical condition, drug abuse, medication, or toxin exposure. Subsequently, evaluation for a primary psychiatric disorder should follow. Assessment typically inventories a woman's ethnic, cultural, religious, and social backgrounds and includes a frank discussion about her current sexual partner(s) and sexual expectations. Clinical judgment should take into account the patient's age and sexual experience, symptom frequency and chronicity, and determine whether a woman perceives her symptoms as distressing or impairing (American Psychiatric Association, 2000a). Importantly, a woman should be asked if the sexual difficulty has always been present or has developed only within a certain time period, and if it persists across all situations or only appears in certain circumstances. Finally, referral to a psychiatrist or psychologist may be indicated for a thorough psychiatric interview.

Treatment of Sexual Dysfunction

Multidisciplinary treatment is ideal for patients with sexual dysfunction. A team would typically include the referring physician, gynecologist, psychologist, and a nurse-specialist. In organic disorders, it may be necessary to include specialists in urology, gastroenterology, and anesthesiology. Psychological approaches usually include some combination of sexual education, communication enhancement, identification of emotional and cultural factors, cognitive-behavioral therapy, and couples therapy.

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PEDIATRIC GYNECOLOGY: INTRODUCTION

Pediatric gynecology is a unique subspecialty which encompasses knowledge from various specialties including general pediatrics, gynecology, and reproductive endocrinology, as well as pediatric endocrinology and pediatric urology. Treatment of a particular patient may therefore require the collaboration of clinicians from one or more of these areas.

Gynecologic disorders in children can differ greatly from those encountered in the adult female. Even the simple physical examination of the genitalia differs significantly. A thorough understanding of such differences can aid in clarifying and diagnosing the variety of gynecologic abnormalities seen in this age group.

PHYSIOLOGIC CHANGES WITH PUBERTY

Puberty marks the normal physiologic transition from childhood to sexual and reproductive maturity. Each landmark of hormonal and anatomic change during this time represents a spectrum of what is called "normal".

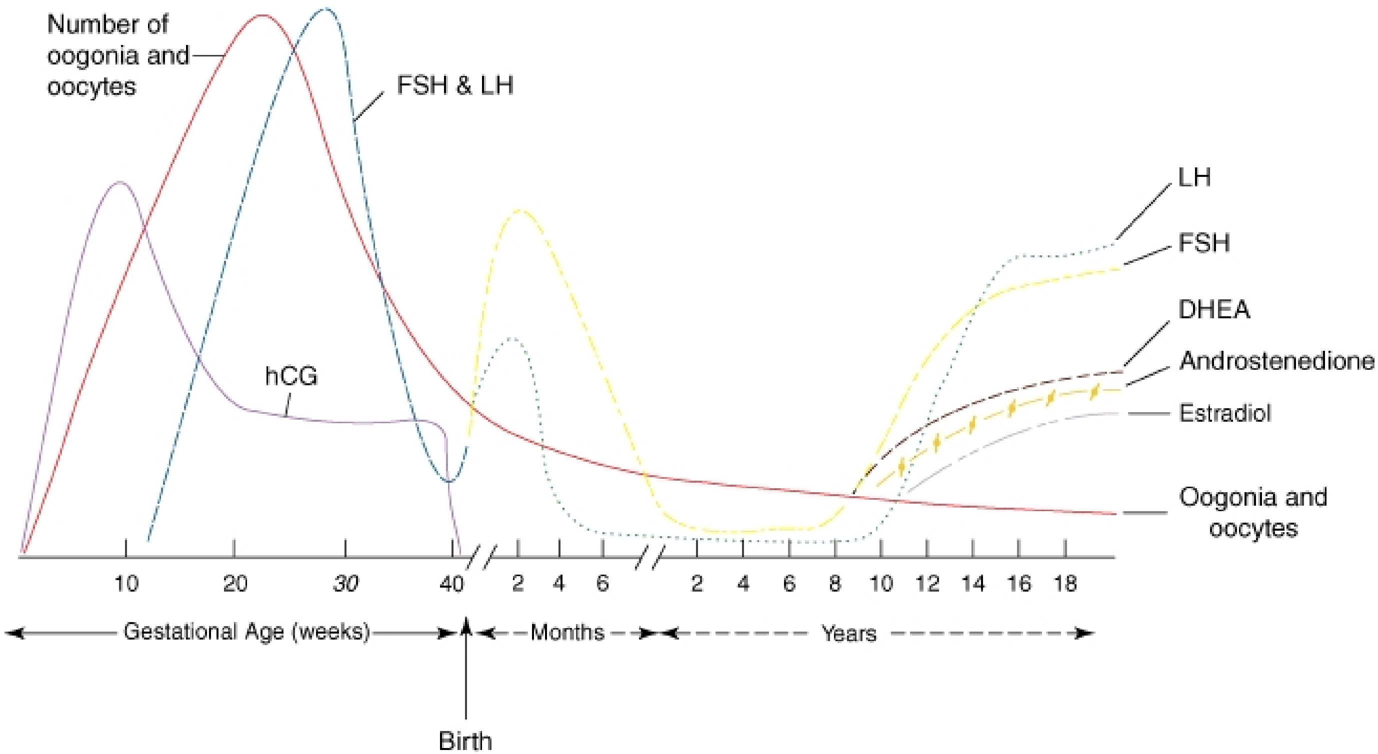
With puberty, primary sexual characteristics of the hypothalamus, pituitary, and ovaries initially undergo an intricate maturation process. This maturation leads to the complex development of secondary sexual characteristics involving the breast, sexual hair, and genitalia, in addition, to a limited acceleration in growth.

Hypothalamic-Pituitary-Ovarian Axis

A carefully orchestrated cascade of events unfolds in the neuroendocrine system that regulates subsequent development of the female reproductive system (see Chap. 15, Steroidogenesis Across the Life Span).

In utero, gonadotropin-releasing hormone (GnRH) neurons develop in the olfactory placode. These neurons migrate through the forebrain to the arcuate nucleus of the hypothalamus by 11 weeks of gestation. They form axons that extend to the median eminence and to the capillary plexus of the pituitary portal system (Ronnekliev, 1990; Schwanzel, 1989; Silverman 1987). Gonadotropin-releasing hormone, a decapeptide, is influenced by higher cortical centers and is released in a pulsatile fashion into the pituitary portal plexus. As a result, the GnRH "pulse generator" stimulates secretion of gonadotropins, that is, follicle-stimulating hormone (FSH) and luteinizing hormone (LH), from the anterior pituitary by midgestation. In turn, the pulsatile release of gonadotropins stimulates ovarian synthesis and release of gonadal steroid hormones. Concurrently, accelerated germ cell division and follicular development begins, resulting in the creation of 6 to 7 million oocytes by 5 months' gestation. By late gestation, gonadal steroids exert a negative feedback upon both the pituitary gonadotropins and hypothalamic GnRH secretion. During this time, the oocyte number decreases through a process of gene-related apoptosis to reach 1 to 2 million by birth (Fig. 14-1) (Vaskivuo, 2001).

FIGURE 14-1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Variation in oocyte number and hormone levels during the prenatal and postnatal periods. DHEA = dehydroepiandrosterone; FSH = follicle-stimulating hormone; hCG = human chorionic gonadotropin; LH = luteinizing hormone.

At birth, FSH and LH levels rise abruptly in response to the fall in placental estrogen, and gradually decline within the first few months of life to reach prepubertal levels by age 1 to 4 years. This transient rise in gonadotropin levels, followed by an increase in gonadal steroid levels, is thought to explain instances of neonatal breast budding and minor bleeding from endometrial shedding.

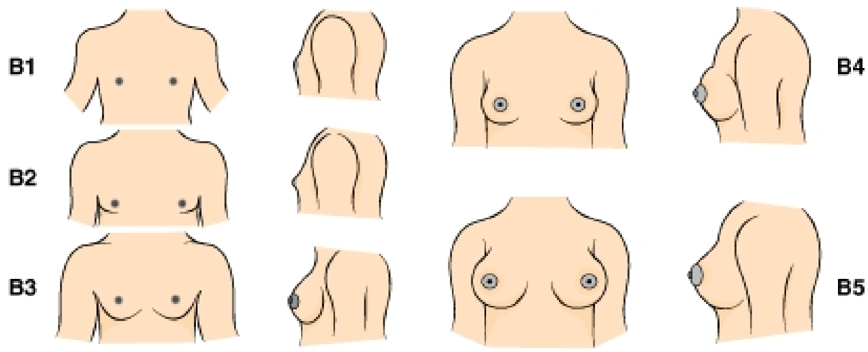
The childhood years are thus characterized by low plasma levels of FSH, LH, and estradiol. However, studies suggest that the GnRH pulse generator is exquisitely sensitive to minute amounts of gonadal steroids (Plant, 1994). True central precocious puberty may develop as a result of premature activation of the GnRH pulse generator.

During childhood, the ovary increases in size and undergoes active follicular growth and atresia. As a result of this attrition, by puberty only 300,000 to 500,000 oocytes remain (Speroff, 2004).

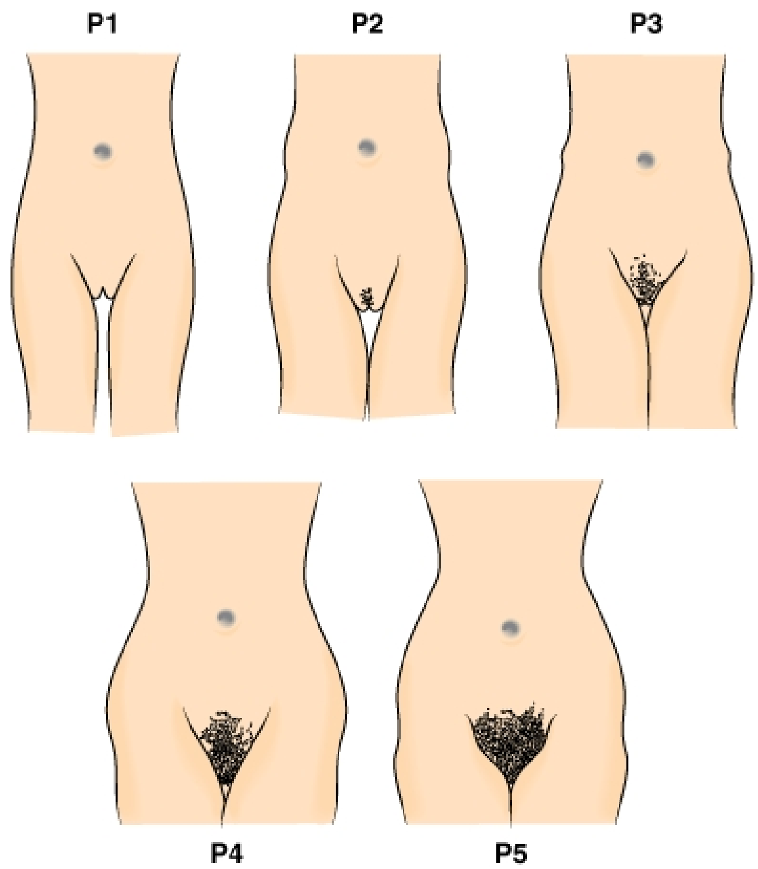
Pubertal Changes

Initial pubertal changes occur between the ages of 8 and 13 years in most North American females (Tanner, 1985). Changes before or after are categorized as either precocious or delayed puberty and warrant evaluation. At approximately age 10 to 12 years, breast budding, termed *thelarche,* is the first physical sign in 90 percent of girls. Alternatively in a minority, pubic hair growth, known as *pubarche* develops first. Marshall and Tanner (1969) recorded breast and pubic hair development in 192 English schoolgirls and created what we now know as the *Tanner stages* (Fig. 14-2). Following breast and pubic hair growth, adolescents, during a 3-year span from ages 10.5 to 13.5 years, undergo an accelerated increase in height, termed a *growth spurt* . The mean age of menarche in white girls is 12.7 years and 6 months earlier, or 12.1, in black girls (Tanner, 1973).

FIGURE 14-2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Tanner stages of female breast and pubic hair development. Stages B1 through B5 reflect stages of thelarche, whereas P1 through P5 depict those of pubarche.

GYNECOLOGIC EXAMINATION

An adolescent who has reached the age of 18 may consent to medical examination and treatment. Prior to this age, a minor child must have the consent of a parent or legal guardian (except in emergency) for examination and treatment.

A routine yearly examination of a child by their pediatrician will generally include a brief examination of the breasts and external genitalia. If visible externally, congenital anomaliesâ€”such as imperforate hymen may be identified during this examination. Alternatively, if parent or child has a specific complaint regarding vulvovaginal pain, rash, bleeding, discharge, or lesion, a gynecologic examination is directed toward the area of concern.

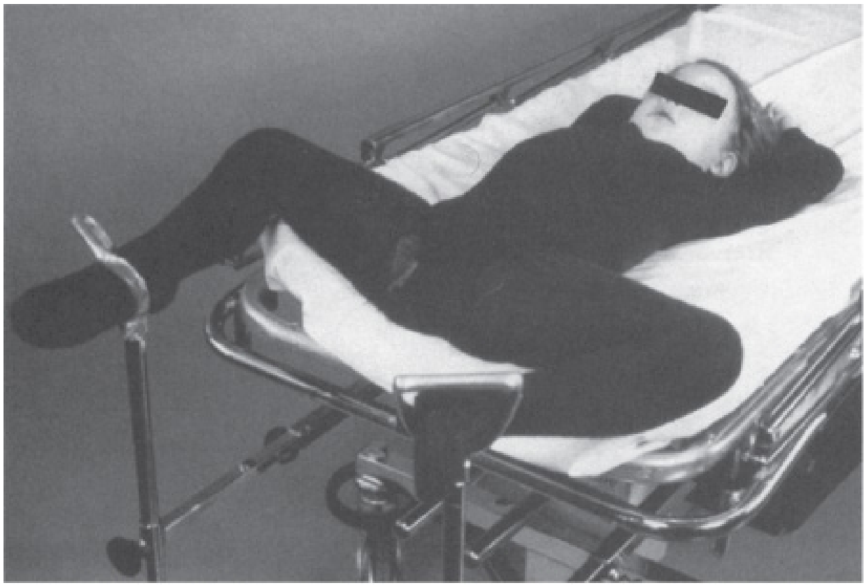
Importantly, a parent or guardian should be present at the examination. This allows a child to understand that the examination is sanctioned. Moreover, clinicians can use this opportunity to inform a parent about findings and potential treatment. This may also be an opportune time to emphasize points regarding inappropriate genital touching and the importance of parental notification if this occurs. In the mid-to-late teenage years, however, an adolescent may prefer, for privacy reasons, not to be examined with a parent present.

"Child-friendly" objects in the examination room such as posters, books, toys, and pictures and distracting conversation can ease fears and significantly aid in examination of the young female (Kass-Wolff, 2003). Similarly, using an anatomically appropriate doll to explain the examination and having the child repeat the procedure on the doll may decrease anxiety.

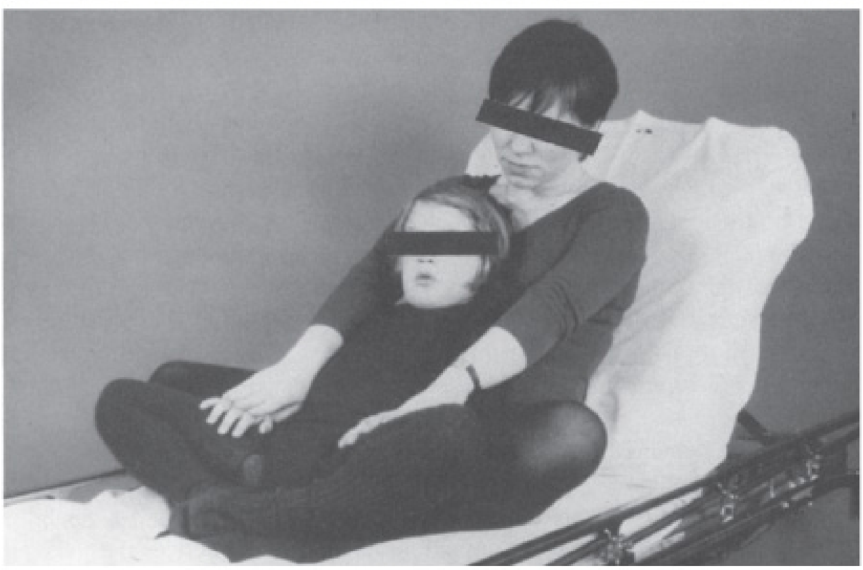
The examination begins with a less-threatening approach of checking the ears, throat, heart, and lungs. Breasts are inspected. The external genital examination is best performed with the child in a frog-leg or knee-chest position to improve visualization. Occasionally, the patient may feel more comfortable sitting in a parent's lap. Sitting on a chair or examination table, the parent allows the child's legs to straddle the parent's thighs (Fig. 14-3).

FIGURE 14-3

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

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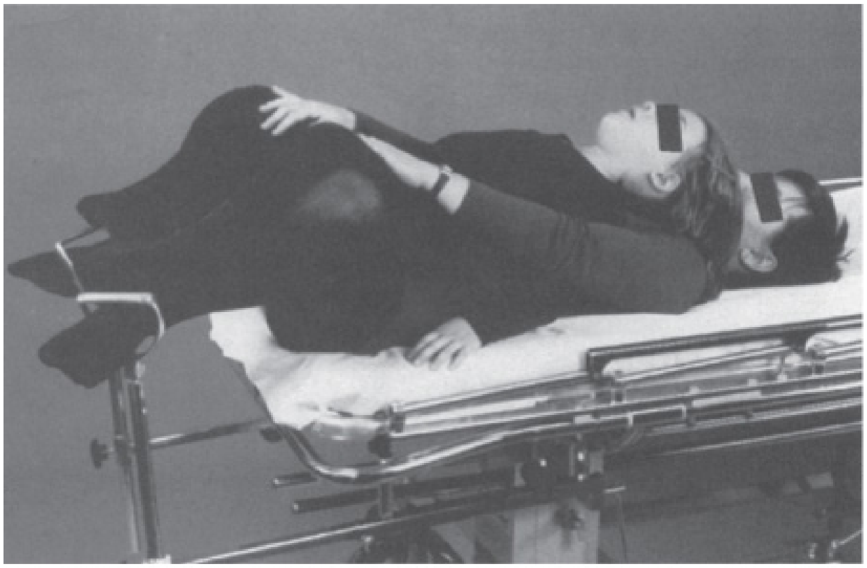


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Various positions for examination of the pediatric patient. *(From Emans, 1998, with permission.)*

Once the child is optimally positioned, each labia may be gently held with a thumb and forefinger and pulled toward the examiner and laterally. In this manner, the introitus, hymen, and lower portion of the vagina are inspected (Fig. 14-4). An internal examination is rarely necessary unless a foreign body, tumor, or vaginal bleeding is suspected. This evaluation is best accomplished under general anesthesia in an ambulatory care center. Vaginoscopy may be performed using a hysteroscope or cystoscope to provide illumination as well as irrigation (Baldwin, 1995; Pokorny, 1997). During vaginoscopy, normal saline is used as the distension medium. The labia majora are manually approximated to occlude the vagina and achieve distention of the vaginal canal.

FIGURE 14-4

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photograph of normal prepubertal genitalia. *(From The North American Society for Pediatric and Adolescent Gynecology, 2001, with permission.)*

PROBLEMS IN PEDIATRIC GYNECOLOGY

Labial Adhesion

Adhesion between the labia minora begins as a small posterior midline fusion, which is usually asymptomatic. This fusion may remain an isolated minor finding or may progress toward the clitoris to completely close the vaginal orifice. Also termed *labial agglutination* , this adhesion develops in 1 to 5 percent of prepubertal girls and in approximately 10 percent of female infants within the first year of life (Berenson, 1992; Christensen, 1971).

The cause of labial adhesion is unknown, although hypoestrogenism is implicated. This fusion typically develops in a low-estrogen environmentâ€”it is seen in infants and young girls, and tends to undergo spontaneous resolution at puberty (Jenkinson, 1984). Additionally, erosion of the vulvar epithelium is thought to underlie some cases of labial adhesion. For example, adhesion has been found in association with vulvar irritation such as lichen sclerosus, herpes simplex viral infections, and with vulvar trauma following sexual abuse (Berkowitz, 1987).

The diagnosis is made by visual inspection of the vulva. The labia majora appear normal, whereas the labia minora are fused with a distinct thin line of demarcation or *raphe* between them. In severe cases, agglutination leaves only a ventral pinhole meatus between the labia. Located immediately beneath the clitoris, this small opening may lead to urinary dribbling as urine pools behind the adhesion. In these cases, urinary tract infection or urethritis may develop (Fig. 14-5).

FIGURE 14-5

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Labial adhesion. The labia minora are agglutinated in the midline. *(From The North American Society for Pediatric and Adolescent Gynecology, 2001, with permission.)*

The treatment of labial adhesions varies according to the degree of scarring and symptoms. In many instances, if the patient is asymptomatic, no treatment is necessary, as the adhesion will typically resolve spontaneously with the rise of estrogen levels at puberty. Extensive adhesion with urinary symptoms, however, will require treatment with an estrogen cream. Estradiol (Estrace, Warner Chilcott, Rockaway, NJ) or alternatively, conjugated equine estrogen (Premarin, Wyeth, Madison, NJ) creams may be applied to the fine, thin raphe twice daily for 2 weeks. This is followed by daily applications for an additional 2 weeks. A generous pea-sized amount of cream is placed with a finger or cotton-tipped applicator to the raphe. With each application, gentle outward traction is exerted on the labia majora to help separate the adhesion. Similarly, light pressure may also be applied with the cotton applicator itself, as tolerated. After adhesion separation, petroleum jelly (Vaseline, Unilever, Englewood Cliffs, NJ) or vitamins A and D ointment (A&D ointment, Schering-Plough HealthCare Products, Berkeley Heights, NJ) may be applied nightly for 6 months to decrease the risk of recurrence. If the adhesion reforms during the subsequent months or years, the process may be similarly repeated. Occasionally, with overuse of estrogen cream, minor breast budding may develop, at which point topical treatment is discontinued.

Manual separation of labial adhesion in an outpatient setting without analgesia is not advised, as significant pain and emotional trauma to the child may result. In addition, recurrence is much more common. However, if adhesions persist despite consistent use of estrogen cream as described above, labia minora separation may be attempted several minutes after applying 5-percent lidocaine ointment to the adhesion raphe.

If separation is not easily accomplished or tolerated by a child, then surgical separation is recommended in an operating room under general anesthesia as an outpatient procedure. Division of the fused labia, also termed *introitoplasty* , involves a midline incision, with suturing of the skin to the underlying mucosa with absorbable suture (Capraro, 1972). To prevent repeated agglutination after surgery, an estrogen cream should be applied nightly for 2 weeks, followed by an emollient cream nightly for at least 6 months.

Vulvitis

ALLERGIC, CONTACT, AND IRRITATIVE DERMATITIS

Inflammation of the vulva may develop in isolation or in association with vaginitis. In such cases, prepubertal girls may complain of vulvar discomfort, dysuria, and itching. Although the underlying pathophysiologies of allergic, contact, and irritative dermatitis vary, the clinical appearance is usually similar. In affected females, vesicles or papules form on bright red edematous skin (Fig. 14-6). In chronic cases, however, scaling, skin fissuring, and lichenification may be noted. In response, a detailed history should be directed to the level of hygiene, degree of continence, and exposure to potential skin irritants. Frequently, children may develop diaper dermatitis as a result of urine and stool exposure. Corrective measures include attempts to keep the skin dry by more frequent diaper changes or by application of emollient creams, such as Vaseline or A&D ointment, to create a barrier against moisture.

FIGURE 14-6

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Diaper rash dermatitis and secondary candidiasis in a girl receiving antibiotic therapy. *(From Wolff, 2007, with permission.)*

Significant pruritus may develop from contact or allergic vulvitis. Typical offending agents include bubble baths and soaps, laundry detergents, fabric softeners and dryer sheets, bleach, and perfumed or colored toilet paper. Topical creams, lotions, and ointments used to soothe an area may also be an irritant to some children. For most, removing the offending agent and encouraging once- or twice-daily sitz baths is sufficient. These baths consist of placing two tablespoons of baking soda in warm water and soaking for 20

minutes. If itching is severe, an oral medication may be prescribed such as hydroxyzine hydrochloride (Atarax, Pfizer, New York, NY) 2 mg/kg/d divided in four doses, or application of a 2.5-percent topical hydrocortisone cream twice daily for 1 week.

LICHEN SCLEROSUS

Additionally, vulvitis may be caused by lichen sclerosus, which similarly to labial adhesions, can develop concurrently with hypoestrogenism or with inflammation. The pathophysiology is unknown, but development of lichen sclerosus in monozygotic twin girls suggests a genetic role (Meyrick Thomas, 1986). Patients may complain of intense itching, discomfort, bleeding, excoriations, and dysuria. The vulva displays hypopigmentation; atrophic, parchment-like skin; and occasional fissuring (see Fig. 4-1). Lesions are usually symmetrical and may form an hour-glass appearance around the vulva and perianal areas. Diagnosis typically relies on visual inspection; however, rarely a vulvar biopsy may be warranted if the classic skin changes are absent.

Treatment consists of topical corticosteroid cream such as 2.5-percent hydrocortisone, applied nightly to the vulva for 6 weeks. If improvement is noted, the dose may be lowered to 1-percent hydrocortisone and continued for 4 to 6 weeks. Thereafter, strict attention to hygiene and use of petroleum-based ointments is recommended. Severe cases will require a more potent corticosteroid such as clobetasol propionate (Temovate, GlaxoSmithKline, Philadelphia, PA), 0.05 percent applied twice daily for 2 weeks. This initial dosing is followed by an individualized regimen, which slowly tapers the dose to a once-weekly bedtime application.

INFECTION

Some common infectious organisms that may cause prepubertal vulvitis include group A β-hemolytic *Streptococcus, Candida* species, and pinworms. Group A β-hemolytic streptococci may present with a bright beefy-red vulva and introitus. A child may have symptoms of dysuria, vulvar pain, pruritus, or bleeding. In most cases, vulvovaginal culture and clinical examination typically lead to diagnosis. Group A β-hemolytic *Streptococcus* may be treated with a first- generation penicillin or cephalosporin or other appropriate antibiotic for 2 to 4 weeks.

Candidiasis is rarely seen in nonestrogenized prepubertal girls. It more often develops during the first year of life, after a course of antibiotics, or in females with juvenile diabetes or an immunocompromised condition. Diagnosis is assisted by visual inspection of a reddened, raised rash with well-demarcated borders and occasional satellite lesions. Microscopic examination of a vaginal sample prepared with 10-percent potassium hydroxide (KOH) will help identify hyphae (see Fig. 3-15). Treatment consists of twice-daily vulvar application of antifungal creams such as clotrimazole, miconazole, or butaconazole for 10 to 14 days or until the rash is cleared.

Enterobius vermicularis , also known as the *pinworm* , can be a source of intense vulvar itching, particularly at night. Nocturnal pruritus results from an intestinal infection with these 1-cm long, threadlike white worms that often exit the anus at night (Pierce, 1992; Zeiguer, 1993). By inspecting this area with a flashlight at night when the child is asleep, parents may identify worms exiting the anus. The Scotch-tape test entails pressing a piece of tape to the perianal area in the morning, affixing the tape to a slide, and visualizing eggs with microscopy. Treatment consists of mebendazole (Vermox, Janssen-Cilag, Titusville, NJ), 100 mg orally in a single dose and repeated after 1 week.

Physiologic Discharge

Physiologic discharge is often seen transiently in the newborn as a result of exposure to maternal estrogen in utero. This usually appears as a clear to whitish mucous discharge. Also in the first few days after birth, the endometrium may undergo transient shedding and a bloody discharge is seen.

Vulvovaginitis

Vulvovaginitis is one of the most common gynecologic problems of prepubertal girls. Three fourths of cases of vulvovaginitis in this age group are nonspecific, with culture results yielding normal flora. Alternatively, several infectious agents, discussed subsequently, may be identified.

NONSPECIFIC VULVOVAGINITIS

Several months after birth, as estrogen levels wane, the vulvovaginal epithelium becomes thin and atrophic. As a result of this change, the vulva and vagina are more susceptible to irritants and infections until puberty.

More than 50 percent of visits to the pediatric gynecologist involve vulvovaginal complaints (Emans, 1998). The pathogenesis is not well defined, but known instigating factors that can lead to nonspecific vulvovaginitis are included in Table 14-1. Symptoms include itching, vulvar redness, discharge, dysuria, and odor. Most children and adolescents who are not sexually active tolerate speculum examination poorly, but vaginal swab for bacterial culture is typically comfortably obtained. In cases of nonspecific vulvovaginitis, cultures usually only isolate normal vaginal flora. Culture results revealing bowel flora suggest contamination with fecal aerobes.

Table 14-1 Causes of Vulvovaginitis in Children
Poor vulvar hygiene
Inadequate front-to-back wiping after bowel movements
Lack of labial fat pads and labial hair
Short distance from the anus to the vagina
Non-estrogenized vulvovaginal epithelium
Foreign body insertion into the vagina
Chemical irritants such as soaps, bubble baths, or shampoos
Co-existent eczema or seborrhea
Chronic disease and altered immune status
Sexual abuse

Treatment is directed toward correction of the underlying cause. Itching and inflammation may be relieved with the use of a low potency topical corticosteroid (hydrocortisone, 1 or 2.5 percent). Occasionally severe itching can lead to a secondary bacterial infection that requires treatment with an antibiotic. Antibiotics commonly used include amoxicillin, an amoxicillin plus clavulanic acid combination, or a similar cephalosporin, given during a 7- to 10-day course.

INFECTIOUS VULVOVAGINITIS

Infectious vulvovaginitis often presents with a malodorous, yellowish or greenish purulent discharge, and vaginal cultures are routinely obtained in these cases. The respiratory pathogen, group A β-hemolytic *Streptococcus* , is the most common specific infectious agent found in prepubertal females and is isolated from 7 to 20 percent of girls with vulvovaginitis (Pierce, 1992; Piippo, 2000). Treatment of group A β-hemolytic *Streptococcus* consists of amoxicillin, 40 mg/kg taken three times daily for 10 days. Less frequently, other respiratory pathogens found include *Haemophilus influenzae, Staphylococcus aureus* , and *Streptococcus pneumoniae* . Enteric pathogens such as *Shigella* and *Yersinia* species may also be found by culture of vaginal discharge. Classically, *Shigella* species incite a mucopurulent bloody discharge, which typically follows diarrhea caused by the same organism. Treatment is with trimethoprim-sulfamethoxazole (TMP-SMZ), 6 to 10 mg/kg/d orally, divided every 12 hours (Bogaerts, 1992).

Sexual abuse may result in infections, including those caused by *Neisseria gonorrhoeae, Chlamydia trachomatis* , herpes simplex virus (HSV), *Trichomonas vaginalis* , and human papillomavirus (HPV) (see Chap. 3). The clinical presentation of each mirrors the infectious findings in adults. Child protective services should be notified of any child found to have a sexually transmitted disease.

Genital Trauma

The prepubertal vulva is less protected from blunt injury due to the lack of labial fat pads (Fig. 14-7). In addition, children are more physically active, thereby increasing the risk of trauma. Fortunately, most injuries to the vulva are blunt, minor, and accidental. Sharp-object penetration, however, may cause more serious injury to the vulvovaginal area. Sexual or physical abuse should also be considered in many cases of genital trauma. Management of genital trauma is discussed in Chapter 4, Vulvovaginal Trauma.

FIGURE 14-7

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Straddle injury of the vulva with hematoma formation. *(From The North American Society for Pediatric and Adolescent Gynecology, 2001, with permission.)*

Ovarian Tumors

Ovarian tumors are the most common neoplasm found in childhood (Breen, 1977). They may be found prenatally during maternal sonographic evaluation, as well as during prepubertal years and adolescence. Although most are benign, approximately 1 percent of all malignant tumors in this age group are of ovarian origin (Breen, 1977, 1981).

FETAL AND NEONATAL OVARIAN CYSTS

Most fetal and neonatal ovarian cysts are identified incidentally during antepartum maternal sonographic examination. Although the true incidence of fetal ovarian cysts is not known, some cystic development has been reported in 30 to 70 percent of fetuses (Brandt 1991; Lindeque, 1988). Most fetal and neonatal cysts result from maternal hormonal stimulation in utero. They are typically unilateral, asymptomatic, and tend to regress spontaneously by 4 months of age, whether they are simple or complex. The risk of malignancy in fetal and neonatal ovarian cysts is low, although rupture, intracystic hemorrhage, visceral compression, and torsion followed by autoamputation of the ovary or adnexa may be seen.

For uncomplicated fetal or neonatal cysts measuring less than 5 cm in diameter, the management is observation and sonographic examination every 4 to 6 weeks (Bagolan, 2002; Murrray, 1995; Nussbaum, 1988; Spence 1992). For simple cysts measuring greater than 5 cm, percutaneous cyst aspiration may be considered to prevent torsion (Bryant, 2004; Salkala, 1991). Large complex ovarian cysts that do not regress require surgical excision.

PREPUBERTAL OVARIAN CYSTS

Ovarian cysts may develop during the neonatal period and infancy. These result from the postnatal gonadotropic surge seen with the withdrawal of maternal hormones after birth. Most cysts are simple, asymptomatic, and tend to regress within several months. However, ovarian neoplasms found in childhood are most often germ cell tumors (see Chap. 36) (Lack, 1984).

Presenting symptoms in children with ovarian cysts are varied. Asymptomatic cysts may be discovered incidentally during abdominal examination or during sonographic examination for some other indication. Enlarging cysts may cause increased abdominal girth or chronic pain. Hormone-secreting cysts may lead to isosexual or heterosexual precocious puberty. Moreover, rupture, hemorrhage, or torsion may precipitate acute abdominal pain, similar to that seen in adults.

In the older adolescent and adult, transvaginal sonography is the preferred tool to diagnose ovarian tumors. However, a prepubertal child will not tolerate examination with a transvaginal probe. Therefore in this age group, transabdominal pelvic sonography is most frequently used. Computed tomography is helpful if a mature cystic teratoma (dermoid cyst) is suspected, as fat is better appreciated with this modality. Although magnetic resonance (MR) imaging is preferred for evaluation of congenital mÃ¼llerian anomalies, it is less helpful than pelvic sonography for ovarian mass determination.

As with those of the fetal and neonatal periods, small simple ovarian cysts without septation or internal echoes may be monitored with serial sonographic examination. Most less than 5 cm in size will resolve within 1 to 4 months (Thind, 1989). Persistent or enlarging cysts warrant surgical intervention, and laparoscopy is the preferred method. Optimal management includes fertility-sparing ovarian cystectomy with preservation of any normal ovarian tissue.

Breast Development and Disease

At puberty, under the influence of ovarian hormones, the breast bud grows rapidly. The epithelial sprouts of the mammary gland branch further and become separated by increasing deposition of fat.

Newborns may have some minor breast budding due to transplacental passage of maternal hormones in utero. Similarly, newborn breasts may produce *witches' milk* , which is a bilateral white nipple discharge, also as a result of maternal hormone stimulation. Both effects are transient and most often diminish during several weeks to months.

Breast development, termed *thelarche* , begins in most girls between the ages of 8 and 13 years. Thelarche prior to age 8 or lack of breast development by age 13 is considered abnormal and should be investigated.

BREAST EXAMINATION

A breast evaluation and examination begins in the newborn period and extends through the prepubertal and adolescent years, as abnormalities can develop in any age group. Assessment includes inspection for accessory nipples, infection, lipoma, fibroadenoma, and premature thelarche.

POLYTHELIA

Accessory nipples, also termed *polythelia* , is common and noted in 1 percent of patients. Most frequently, a small areola and nipple are found along the embryonic milk line, which extends from the axilla to the groin (Latham, 2006; Loukas, 2007).

Accessory nipples are usually asymptomatic, and excision is not required. Rarely, however, they may contain glandular tissue, which can lead to pain, nipple discharge, or development of fibroadenomas (Aughsteen, 2000; Oshida 2003).

PREMATURE THELARCHE

Thelarche may begin before the age of 8 years in some girls and is most commonly seen in girls aged less than 2 years (Fig. 14-8). This early breast maturation is termed *premature thelarche* . It differs from precocious puberty in that it is benign, self-limited, and develops in isolation, without other signs of pubertal development. Premature thelarche is suspected if a girl's height falls within established percentile curves and minimal breast tissue growth or nipple maturation is noted during surveillance. Monitoring body growth and breast changes alone may suffice, but in those with increased height or weight or with other pubertal changes, additional testing for precocious puberty is warranted. Accordingly, analysis of a girl's growth curve and Tanner stage, radiographic bone age study, and gonadotropin measurement may each be indicated. Bone age can be determined at many skeletal sites, and

the left hand and wrist are by far the most commonly used. Premature thelarche is suggested if the bone age falls within 1 year of chronologic age (normal). However, if the bone age is advanced by 2 or more years, puberty has begun and evaluation of precocious puberty is warranted. Serum estradiol levels may be slightly elevated in girls with premature thelarche and are seen more commonly in very-low-birth-weight infants (Escobar, 1976; Ilicki, 1984; Klein 1999; Nelson 1983). In most cases, premature breast development regresses or stabilizes, and treatment consists of reassurance with careful surveillance for other signs of precocious puberty.

FIGURE 14-8

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Premature thelarche. *(From The North American Society for Pediatric and Adolescent Gynecology, 2001, with permission.)*

BREAST ASYMMETRY

Asymmetrical breast growth may be seen commonly during early breast development stages in adolescent girls aged 13 to 14 years. A thorough examination should be performed to check for the presence of a breast mass such as a fibroadenoma, cyst, or infection. If no such pathologic process exists, yearly examinations are performed to determine the extent of asymmetry.

The etiology of breast asymmetry is not known, although there have been cases of sports injuries or surgical trauma occurring during early breast development that may have led to unequal growth (Goyal, 2003; Jansen, 2002). Moreover, a strong association of asymmetry and tuberous breast formation has been noted (DeLuca-Pytell, 2005).

In most cases, asymmetry will resolve by completion of breast maturity (Templeman, 2000). Therefore, a decision about surgical intervention involving augmentation or reduction mammoplasty is not made until full breast growth is attained. Until that time, adolescents may be fitted with padded bras or even prosthetic inserts to ensure symmetry when fully clothed. Although most

adolescents with minor breast asymmetry choose not to undergo surgical intervention, others may elect to visit with a plastic surgeon to discuss options, particularly if asymmetry is pronounced.

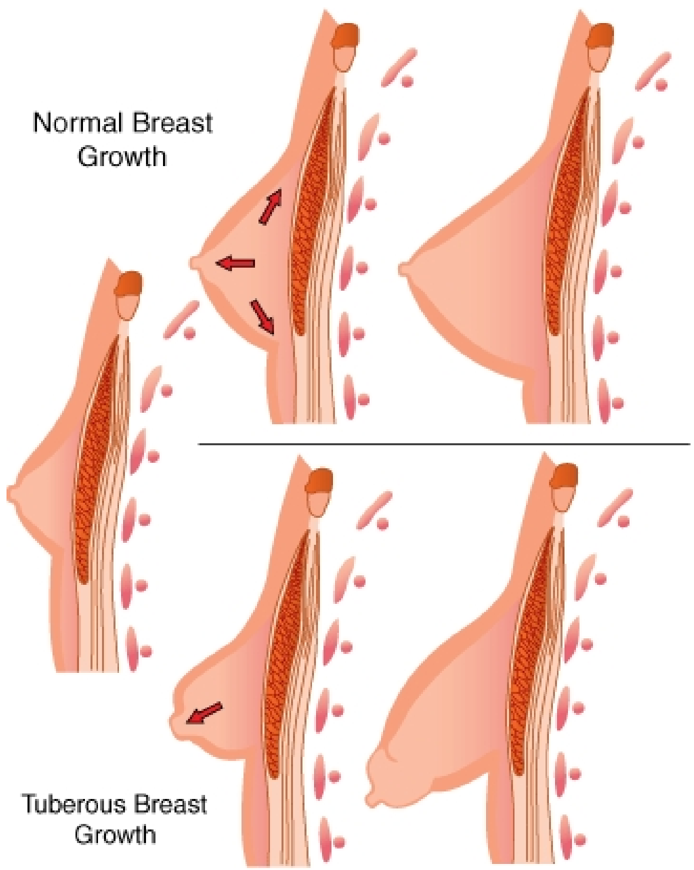
BREAST HYPERTROPHY

Rarely, adolescents develop extremely large breasts without concurrent large breast masses. Breast hypertrophy can be symptomatic and complaints may include back pain, shoulder discomfort from bra-strap pressure, and kyphosis, not to mention the social stigmata that can cause psychological distress. These young women will often seek reduction mammoplasty, but surgery should be delayed until breast growth is completed, as determined by serial breast measurements, typically between the ages of 15 to 18 years.

TUBEROUS BREASTS

With normal breast development, ventral growth projects the areola forward and peripheral growth enlarges the breast base. In some adolescents, the fascia is densely adhered to the underlying muscle and fails to be separated from its muscular layer by laterally expanding breast tissue (Fig. 14-9). This restricts peripheral expansion of the breast base, and breast growth is directed forward. Termed *tuberous breasts* , these breasts display a tubular appearance that is characterized by a narrowed breast base, elevation of the skin fold under the breast, and hypoplastic development of the lower portion of the breast. To optimize surgical correction of this deformity, Grolleau and colleagues (1999) developed a classification system based on the number of breast quadrants involved. Type I defects involve only the medial lower breast quadrant; type II, both lower quadrants; and type III, all quadrants.

FIGURE 14-9



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Comparison of normal and tuberous breast development. *(Redrawn from Grolleau, 1999, with permission.)*

Additionally, this type of appearance can result from exogenous hormone replacement. This is often given to girls who lack breast development due to genetic, metabolic, or endocrine conditions. To avoid tuberous development in this setting, hormone replacement is initiated at small dosages and gradually increased over time. For example, conjugated equine estrogen (Premarin), 0.3 mg may be given orally each day for 6 months, followed by incremental dose increases every 6 months, through doses 0.625 mg and 0.9 mg, to finally reach 1.25 mg daily. Medroxyprogesterone acetate (Provera, Pfizer, New York, NY), 10 mg is given orally each day for 12 days of the month to prompt withdrawal menses. Once estrogen dosing has reached 1.25 mg daily, the patient may alternatively be placed on a low-dose oral contraceptive pill.

LACK OF BREAST DEVELOPMENT

Congenital absence of breast glandular tissue, termed *amastia,* is rare. More commonly, a lack of breast development results from low estrogen levels caused by constitutionally delayed puberty, debilitating chronic disease, radiation or chemotherapy, genetic disorders such as gonadal dysgenesis, or extremes of physical activity such as ballet or endurance sports. Treatment is based on etiology. For example, once a competitive athlete completes her career, breast development may begin spontaneously without hormonal treatment. Alternatively, to prompt breast development and prevent osteoporosis, adolescent girls with gonadal dysgenesis will require some form of hormonal replacement, such as that described earlier for the prevention of tuberous breasts.

NIPPLE DISCHARGE

Nipple discharge may present in varied colors, which may indicate their etiology. For example, milky white discharge typifies galactorrhea; cloudy yellow or light-green liquid may indicate infection; and greenish-brown discharge is commonly associated with ductal ectasia. Serosanguinous nipple fluid may reflect an intraductal papilloma or rarely cancer. In general, the pathophysiology and management of these discharges mirrors that of an adult female (see Fig. 12-6).

BREAST CYSTS

When an adolescent complains of a breast lump, often the findings are consistent with fibrocystic changes. These are characterized by patchy or diffuse, band-like thickenings or lumps. As many as 50 percent of women are found to have fibrocystic changes on clinical examination, and the etiology is unknown (Love, 1982).

Sonography may aid in distinguishing between a cystic and solid mass and defining cyst qualities (Garcia, 2000). In contrast, mammography has a limited role in the evaluation of child and adolescent breast tissue. Mammography has limited sensitivity and specificity in young developing breasts, and the dense nature of their breast tissue yields high rates of false-negative results (Williams, 1986).

Actual breast cysts are found on occasion and will usually resolve spontaneously during a few weeks to months. If a cyst is large, persistent, and symptomatic, then fine-needle aspiration may be performed using local anesthesia in an office setting.

BREAST MASSES

Most breast masses in children and adolescents are benign and may include normal but asymmetric breast bud development, fibroadenoma, fibrocyst, lymph node, and abscess. The most common breast mass identified in adolescence is the fibroadenoma, which accounts for 68 to 94 percent of all masses (Daniel, 1968; Goldstein, 1982). Fortunately, breast cancer in pediatric populations is rare, and Neinstein (1994) cited an incidence of cancer in less than 1 percent of breast masses identified in this group. However, primary breast cancer may develop more frequently in pediatric patients with a history of prior radiation, especially to the chest wall. Additionally, metastatic disease should be considered in those with a history of malignancy.

Following identification of a breast mass on physical examination in a young female, sonography is the primary imaging method. Magnetic resonance (MR) imaging is not routinely recommended because of its high cost and limited availability.

Treatment of breast masses includes observation, needle aspiration, and surgical excision. Observation may be appropriate for small asymptomatic lesions considered to be fibroadenomas. Alternatively, in many cases, a tissue diagnosis with a minimally invasive procedure such as fine-needle aspiration is warranted. Additionally, core-needle biopsy with sonographic guidance is another percutaneous option. In any mass not surgically excised, clinical surveillance is recommended to ensure stability of the

mass (Weinstein, 2003). Masses that are symptomatic, large, or enlarging are preferably excised using local or general anesthesia in an ambulatory surgical center.

Mastitis is rare in the pediatric population, and its incidence displays a bimodal distribution. Most mastitis is seen in the neonatal period and to a lesser degree in children older than 10 years. The etiology in these cases is unclear, but the association with breast enlargement during these two periods has been implicated. *Staphylococcus aureus* is the most common isolate, and abscess develops more commonly than in the adult (Faden, 2005). Alternatively in adolescents, infections may be associated with lactation and pregnancy, trauma related to sexual foreplay, shaving periareolar hair, and nipple piercing (Templeman, 2000; Tweeten, 1998). Infections are treated with antibiotics and occasional drainage, if an abscess has formed.

Vaginal Bleeding

Neonates may present with vaginal bleeding during the first week of life due to withdrawal of maternal estrogen at birth. Bleeding typically resolves after a few days. Prepubertal bleeding in a child, however, warrants careful evaluation (Table 14-2).

Table 14-2 Causes of Vaginal Bleeding in Children
Foreign body
Genital tumors
Urethral prolapse
Lichen sclerosus
Vulvovaginitis
Condyloma acuminata
Trauma
Precocious puberty
Exogenous hormone usage

Precocious Puberty

Early pubertal development may be seen in both sexes, but females are more commonly affected, with a gender ratio of 23:1 (Bridges, 1994). For girls, precocious puberty has historically been defined as the development of breast or pubic hair in girls younger than 8 years. However, Herman-Giddens and colleagues (1997) noted that girls in the United States are undergoing pubertal development at younger ages than previously reported. In black girls, puberty begins even earlier. Accordingly, to limit the proportion of girls requiring evaluation for precocious puberty, these investigators and a subsequent pediatric endocrinology task force have suggested modifying the age for evaluation of precocious puberty to younger than age 7 years for white girls and age 6 for black girls who display signs of pubertal development (Herman-Giddens 1997; Kaplowitz, 1999).

Premature pubertal development may result from a variety of etiologies. These causes have been categorized based on the site of pathogenesis and include central precocious puberty, peripheral precocious puberty, heterosexual precocious puberty, and variations of normal puberty. Most girls evaluated for precocious puberty are found to have normal pubertal development that has merely begun prior to standard temporal milestones and does not stem from underlying pathology. However, because many of the underlying etiologies of precocious puberty carry significant sequelae, girls with early pubertal development should be fully evaluated when identified.

CENTRAL PRECOCIOUS PUBERTY (GONADOTROPIN-DEPENDENT)

Early activation of the hypothalamic-pituitary-ovarian axis leads to GnRH secretion, increased gonadotropin formation, and in turn

increased gonadal sex steroid levels. Often termed *true precocious puberty* , central precocious puberty is rare and affects one in 5,000 to 10,000 individuals in the general population (Partsch, 2002). The most common cause of central precocious puberty is idiopathic, however, central nervous systems lesions must be excluded (Table 14-3).

Table 14-3 Common Etiologies of Precocious Puberty
Central(GnRH-dependent)
Idiopathic
Central nervous system (CNS) tumors ▪ Hamartomas ▪ Astrocytomas ▪ Adenomas ▪ Gliomas ▪ Germinomas
CNS infection
Head trauma
Iatrogenic ▪ Radiation ▪ Chemotherapy ▪ Surgical
Malformations of the CNS ▪ Arachnoid or suprasellar cysts ▪ Septo-optic dysplasia ▪ Hydrocephalus ▪ Empty sella syndrome
Peripheral (GnRH-independent)
Congenital adrenal hyperplasia
Testosterone/estrogen-producing tumors ▪ Adrenal/ovarian carcinoma or adenoma ▪ Granulosa cell tumor ▪ Theca cell tumor ▪ Leydig cell tumor
Gonadotropin/hCG-producing tumors ▪ Choriocarcinoma

■ Dysgerminoma ■ Hepatoblastoma ■ Chorioepithelioma ■ Teratoma ■ Gonadoblastoma
Exogenous exposure to androgen or estrogen
Familial male-limited precocious puberty
McCune-Albright syndrome
Ovarian cysts
Hypothyroidism (Van Wyk-Grumbach syndrome)
Aromatase excess syndrome

CNS = central nervous system; GnRH = gonadotropin-releasing hormone; hCG = human chorionic gonadotropin. From Nathan, 2005, with permission.

Symptoms of central precocious puberty are similar to those of normal puberty, with breast development, growth spurt, and eventual menses. However, these are seen at an earlier age (Fig. 14-10). As outlined in Table 14-4, testing includes a left hand and wrist bone age radiographic measurement. Advanced skeletal maturation is seen in affected girls. Serum FSH, LH, and estradiol levels typically fall in the pubertal range. Early in the process, however, FSH and LH may only be elevated in the evenings, and a GnRH stimulation test can be helpful. During GnRH stimulation, GnRH (3.5 μg/kg, not to exceed 100 μg) is infused intravenously, and gonadotropins levels are measured before and at sequential intervals after infusion. Central precocious puberty is confirmed by a rise in serum LH levels following infusion. In contrast, lack of LH and FSH level elevation after infusing GnRH suggests peripheral precocious puberty. Computed tomography and MR imaging of the central nervous system may identify a cerebral abnormality.

Table 14-4 Evaluation of Precocious Puberty
For girls presenting with signs of estrogen excess:
Bone age
FSH, LH, estradiol, TSH
Pelvic sonography
Magnetic resonance imaging of the CNS with contrast medium
For girls presenting with signs of virilization:
Bone age
FSH, LH, estradiol
DHEAS and testosterone
17-Hydroxyprogesterone

Androstenedione
11-Deoxycortisol
A GnRH stimulation test may help differentiate premature thelarche from true central and peripheral precocious puberty.

CNS = central nervous system; DHEAS = dehydroepiandrosterone sulfate; FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone; TSH = thyroid-stimulating hormone.

FIGURE 14-10

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photograph of a girl with precocious puberty. *(From The North American Society for Pediatric and Adolescent Gynecology, 2001, with permission.)*

Treatment goals focus on preventing reduced final adult height and limiting the psychological effects of early pubertal development. Epiphyseal fusion is an estrogen-dependent process. Accordingly, girls with precocious puberty are at risk for early growth plate closure and short stature in adulthood. Treatment consists of a GnRH agonist, which serves to downregulate pituitary gonadotrophs and inhibit FSH and LH release. Estrogen levels drop, and often there is a marked regression of breast and uterine size. If therapy is instituted after menses have begun, they will cease.

Typically, GnRH agonists, such as depot leuprolide acetate (Lupron Depot-PED, TAP Pharmaceuticals, Lake Forest, IL) are administered as intramuscular injection. However, data from a recent phase III trial show, histrelin, a yearly subdermal implant, is effective in sex steroid suppression in girls with central precocious puberty (Eugster, 2007).

PERIPHERAL PRECOCIOUS PUBERTY (GONADOTROPIN-INDEPENDENT)

Less commonly, elevated estrogen levels may originate from a peripheral source such as an ovarian cyst. Termed *peripheral precocious puberty* , this category is characterized by lack of GnRH pulsatile release, low levels of pituitary gonadotropins, yet increased serum estrogen levels.

Although the originating source is variable, the most common cause is granulosa cell tumor, accounting for more than 60 percent of cases (see Chap. 36, Juvenile Granulosa Cell Tumors) (Emans, 1998). Other types of ovarian cysts, adrenal disorders, iatrogenic disorders, and primary hypothyroidism are additional causes (see Table 14-3). McCune-Albright syndrome is characterized by polyostotic fibrous dysplasia, irregular cafÃ©-au-lait spots, and endocrinopathies. Precocious puberty is a frequent finding and results from estrogen production in the ovarian cysts that are common in these girls.

In girls with peripheral precocious puberty, estrogen levels are characteristically elevated, whereas serum levels of LH and FSH are low. Bone age determination shows advanced aging and GnRH stimulation shows no elevation in serum LH levels.

Treatment of peripheral precocious puberty consists of eliminating the estrogen. For those with exogenous exposure, elimination of the estrogen source, such as hormonal pills or creams, is sufficient. An estrogen-secreting ovarian or adrenal tumor will require surgical excision, and hypothyroidism is treated with thyroid hormone replacement. Some success has been found in treating patients with McCune-Albright syndrome with an aromatase inhibitor such as testolactone and letrozole (Feuillan, 1986, 2007).

HETEROSEXUAL PRECOCIOUS PUBERTY

Androgen excess with signs of virilization is rare in childhood (see Chap. 17). Termed *heterosexual precocious puberty* , this condition is most commonly caused by increased androgen secretion from the adrenal gland or ovary. Causes include androgen-secreting ovarian or adrenal tumors, congenital adrenal hyperplasia, Cushing syndrome, and exposure to exogenous androgens. Treatment is directed at correction of the underlying etiology.

VARIATIONS OF NORMAL PUBERTY

Although standardized age guidelines accurately reflect the timing of pubertal development in most girls, others begin development early. Premature thelarche, premature adrenarche, and premature menarche describe the premature pubertal development of breast tissue, pubic hair, and menses, respectively. Each develops in isolation and without other evidence of other pubertal development.

Early breast development without any other signs of puberty is termed *premature thelarche* . Assessment of precocious puberty in these girls reveals bone ages consistent with chronological age. In addition, normal FSH, LH, and estradiol levels, pelvic sonographic examinations, and growth are noted. Treatment consists of careful surveillance and reassurance that the remainder of pubertal development will progress at a normal age.

Adrenarche is the onset of dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS) production from the adrenal zona reticularis, which can be detected at around 6 years. The phenotypic result of adrenarche is development of axillary and pubic hair, termed *pubarche,* which occurs in girls at about age 8 years (Auchus, 2004). *Premature adrenarche* is defined, therefore, as the presence of pubic hair prior to age 8 without evidence of any other signs of estrogenization or virilization. Most girls will have an increased level of DHEAS, which suggests that the adrenal gland is undergoing a premature maturation (Korth-Schutz, 1976). Some girls with premature adrenarche are found to develop polycystic ovarian syndrome in adolescence (Ibanez, 1993; Miller, 1996; Rosenfield, 2007; Siklar, 2007). Others are found to have a partial deficiency of 21-hydroxylase. Therefore, girls presenting with premature adrenarche should be screened with a bone age radiograph, a serum DHEAS level, and an early morning serum 17-hydroxyprogesterone level. Treatment includes reassurance and monitoring at 3- to 6-month intervals for other signs of puberty.

Uterine bleeding that occurs once for several days or monthly, without the presence of other signs of puberty, is termed *premature menarche* . This condition is rare, and other sources of bleeding should be considered and excluded first.

Delayed Puberty

Puberty is considered delayed if no secondary sexual characteristics are noted by age 13, which is more than two standard deviations from the mean age, or if menses are still absent by age 15 (Table 14-5). Delayed puberty affects 3 percent of

adolescents and causes include chronic anovulation, constitutional delay, anatomic abnormalities, hypergonadotropic hypogonadism, and hypogonadotropic hypogonadism (see Chaps. 18 and 16, Classification System) (Albanese, 1995; Ghali, 1994; Malasanoa, 1997). Of these, constitutional delay is the most common (Albanese 1995; Ghali 1994; Layman, 1994). These adolescents present with lack of both secondary sexual characteristics and pubertal growth spurt by age 13 years. The probable cause is a delay in the reactivation of the GnRH pulse generator (Layman, 1994). Patients may be started on low-dose estrogen until puberty progresses, at which point estrogen may be discontinued. During low-dose estrogen treatment, it is not necessary to introduce progesterone withdrawal because in early puberty there is a similarly long period of unopposed estrogen prior to ovulatory cycles.

Table 14-5 Causes of Delayed Puberty
Constitutional (physiologic delay)
Chronic anovulation (polycystic ovarian syndrome)
Anatomic
Imperforate hymen
Transverse vaginal septum
Vaginal and/or cervical agenesis
MÃ¼llerian agenesis (Rokitansky-KÃ¼ster-Hauser syndrome)
Testicular feminization (androgen insensitivity syndrome)
Hypergonadotropic hypogonadism
Gonadal dysgenesis (Turner syndrome)
Pure gonadal dysgenesis (46,XX or 46,XY)
Premature ovarian failure
Idiopathic
Resistant ovary syndrome
Autoimmune oophoritis
Chemotherapy
Radiation
17α-Hydroxylase deficiency
Aromatase deficiency
Galactosemia
Hypogonadotropic hypogonadism
Central nervous system etiologies

Tumors (i.e., craniopharyngioma)
Infection
Trauma
Chronic disease (i.e., celiac disease or Crohn disease)
GnRH deficiency (Kallman syndrome)
Isolated gonadotropin deficiency
Hypothyroidism
Hyperprolactinoma
Adrenal
Congenital adrenal hyperplasia
Cushing syndrome
Addison disease
Psychosocial
Eating disorders
Excessive exercise
Stress, depression
Constitutional delay is the most frequent cause of delayed puberty

GnRH = gonadotropin-releasing hormone.

Sexuality

GENDER IDENTITY

Many couples choose to learn the gender of their baby before delivery, and with highly sensitive sonographic examination, the sex of the baby may be identified with high accuracy as early as 12 to 14 weeks' gestation. Other couples choose to learn the gender of their baby at birth.

Typically, girls are "raised as girls" and boys are "raised as boys". Gender-appropriate clothes and behaviors, as prescribed by the local community, are adopted by the child and reinforced by parental approval. Behaviors in conflict with assigned gender are generally discouraged. However, young children will often explore a variety of behaviors, both masculine and feminine, which are included in the variety of normal experiences in the process of sex-role socialization (Maccoby, 1974; Mischel, 1970; Serbin, 1980).

The task of determining sexual assignment becomes more challenging in cases of ambiguous genitalia in the newborn. Initially, the possibility of life-threatening disease, such as congenital adrenal hyperplasia, should be investigated (see Chap. 18, Congenital Ambiguity of the Genital Tract). Gender assignment may be difficult in many cases of ambiguous genitalia, and is best not performed in the delivery room, but within a few days to weeks, when tests can then identify the problem and a decision can be made.

The final gender assignment in such cases is termed the *sex of rearing,* and reflects the pattern of gender behavior to be emphasized. The final determination of the sex of rearing is based not only on the individual's karyotype, but also on the functional capacity of the external genitalia. For example, boys born with congenital absence of the penis, a rare disorder, are usually raised as females after bilateral orchidectomy and reconstruction of the scrotum to have the appearance of labia. If parental attitudes towards the assigned gender are consistent, most children assume the sex of rearing easily, regardless of their genotype.

ADOLESCENT PERCEPTIONS OF SEXUAL ACTIVITY

Adolescent sexuality develops during a period of rapid change that provides opportunities for adolescents to experience both risk-taking and health-promoting behaviors. Data from the 1995 National Survey of Family Growth reveal that the percentage of teenagers who become sexually active increases steadily after age 13 (Table 14-6) (Abma, 2001).

Table 14-6 Percentages of Sexually Active Teenagers According to Age

Age	Percentage Sexually Active
14	8
15	19
16	32
17	47
18	59
19	70

Research suggests that adolescents view health care providers as an important resource for information and education regarding healthy sexual development. However, many parents and educators oppose sexuality education. Concerns that providing such information will encourage the onset of intercourse, termed *coitarche* , and will increase the frequency of intercourse are typical. On the contrary, several studies have found that such education will actually delay the onset and frequency of sexual activity, increase contraceptive use, and reduce rates of unprotected intercourse (Kirby, 1999, 2001). A national survey in 1999 noted that 75 percent of adolescents attending grades 7 through 12 in public secondary schools reported that they received classes in sexuality education (Hoff, 2000). A large percentage wanted more information on specific topics such as contraception and sexually transmitted diseases (STDs) (46 percent), condom use (30 percent), emotional issues (46 percent), and testing for STDs (51 percent).

Oral sex is now more commonplace among adolescents. The National Survey of Family Growth in 2005 reported that one in four adolescents aged 15 to 19 years who had not had sexual intercourse reported practicing oral sex with a partner. Of those adolescents who practiced sexual intercourse, 83 percent of females and 88 percent of males stated they had engaged in oral sex (Mosher, 2005). Adolescents may see oral sex as an alternative way to maintain their "technical virginity", prevent pregnancy, avoid STDs, or perceive it as a step on the way to engaging in sexual intercourse with a dating partner.

Sexual activity and partner violence appear to have a frequent association in adolescent populations (see Chap. 13, Risk Factors Associated with Domestic Violence). For example, Kaestle and Halpern (2005) noted that violent victimization was more likely to occur in romantic relationships that included sexual intercourse (37 percent) compared with those that did not (19 percent). Abma and colleagues (1997) reported that among sexually active girls aged 15 to 19 years, 25 percent were forced to have nonconsensual intercourse.

CONTRACEPTION

Despite the availability of a wide range of contraceptive options, the United States has 3 million unplanned pregnancies each year, which is one of the highest rates in the industrialized world (Henshaw, 1998). Approximately 1 million of these unintended

pregnancies occur in women using oral contraceptive pills (Piccinino, 1998). Recent trends in contraceptive technology include development of equally effective methods that enhance patient compliance. These new methods include the contraceptive patch, vaginal ring, levonorgesterel-containing intrauterine system, extended-use oral contraceptive pills, and subdermal etonogestrel releasing implant (see Chap. 5, Transdermal Administration). The most commonly used contraceptive by adolescents is the combination oral contraceptive (COC) pill. A survey from the Centers for Disease Control and Prevention in 2002 revealed that of those using birth control, 44 percent used COC pills, 38 percent condoms, 10 percent injectables, and 3 percent implants (Centers for Disease Control and Prevention, 2005).

The role of the clinician caring for sexually active adolescents is twofold: to encourage prevention of unintended pregnancy and to protect against STDs. Ideally, counseling should begin prior to the onset of sexual activity, as approximately one third of adolescents do not use contraception with the first act of intercourse (Committee on Adolescents, 1999). Accordingly, this discussion should include education on the use of emergency contraception (Chap. 5, Emergency Contraception).

Adolescents commonly express concerns about contraceptive services, and these include necessity of a concurrent pelvic examination, short- and long-term contraceptive side effects, and confidentiality. Adolescents should be informed that a pelvic examination is not necessary when a contraceptive is prescribed. Pap smear screening is recommended, however, to begin 3 years after coitarche (see Table 29-3).

Many adolescents hold misperceptions about contraception including beliefs that it may cause infertility or birth defects (Clark, 2001). One survey by the Kaiser Family Foundation revealed that more than 25 percent of adolescents were not aware that oral contraceptives did not protect against STDs.

The Supreme Court has ruled that minors have the right to the availability of contraceptives (Carry v. Population Services International, 431 U.S. 678, 1977). Moreover, current law dictates that all states provide consent to adolescents for treatment of "medically emancipated" conditions such as contraception, STDs, pregnancy, substance abuse, and mental health. These are legally designated medical situations for which an adolescent may receive care without the permission or knowledge of a parent or legal guardian (Akinbami, 2003).

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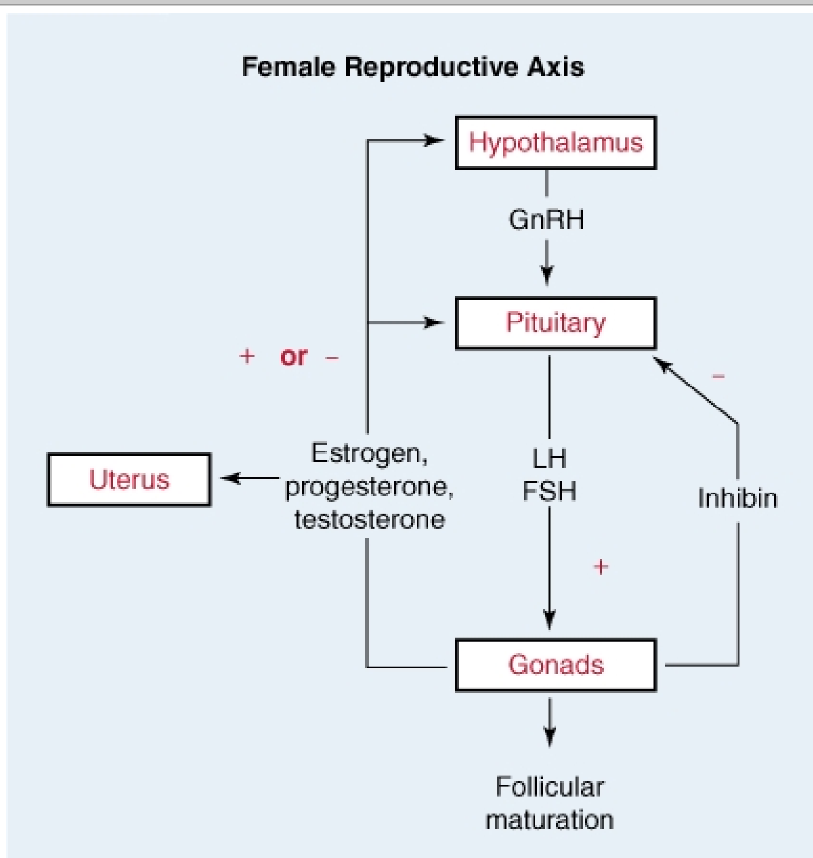
REPRODUCTIVE ENDOCRINOLOGY: INTRODUCTION

Normal reproductive function requires precise quantitative and temporal regulation of the hypothalamic-pituitary-ovarian axis (Fig. 15-1). Within the hypothalamus, specific nuclei release gonadotropin-releasing hormone (GnRH) in pulses. This decapeptide binds to surface receptors on the gonadotrope subpopulation of the anterior pituitary gland. In response, gonadotropes secrete glycoprotein gonadotropins, that is, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), into the peripheral circulation. Within the ovary, LH and FSH bind to theca and granulosa cells to stimulate folliculogenesis as well as ovarian production of an array of steroid hormones (estrogens, progesterone, and androgens), gonadal peptides (activin, inhibin, and follistatin), and growth factors. Among other functions, these ovarian-derived factors feedback to the hypothalamus and pituitary gland to inhibit or, at the midcycle surge, augment GnRH and gonadotropin secretion. The ovarian steroids are also critical for preparing the endometrium for implantation of the embryo if pregnancy ensues.

FIGURE 15-1



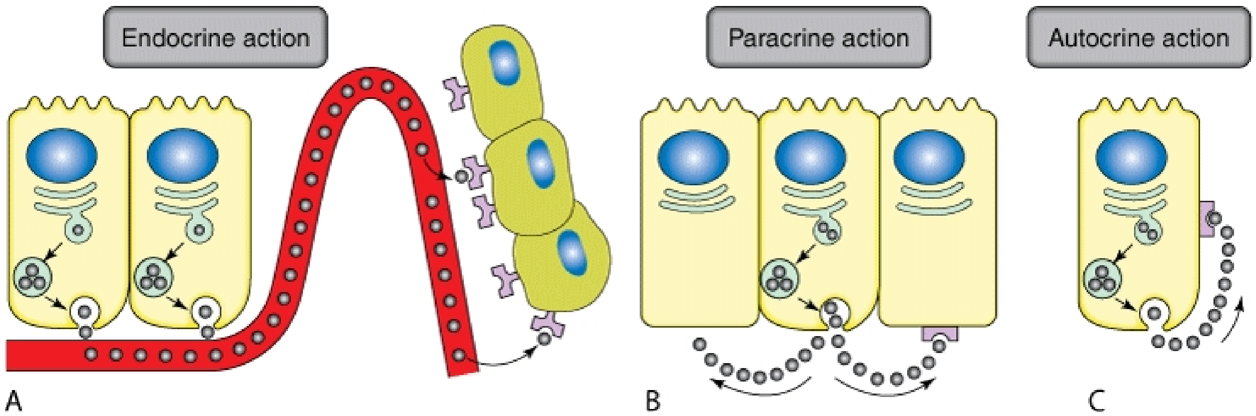
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Diagram depicts positive and negative feedback loops seen with the hypothalamic-pituitary-ovarian axis. Pulsatile release of gonadotropin-

releasing hormone (GnRH) leads to release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary. Effects of LH and FSH result in follicle maturation, ovulation, and production of the sex steroid hormones (estrogen, progesterone, and testosterone). Rising serum levels of these hormones exert negative feedback inhibition on GnRH and gonadotropin release. Sex-steroid hormones vary in their effects on the endometrium and myometrium as discussed in the text. Inhibin, produced in the ovary, has a negative effect on gonadotropin release.

Reproductive endocrinology is the study of hormones and neuroendocrine factors that are produced by and/or affect reproductive tissues. These tissues include the hypothalamus, anterior pituitary gland, ovary, endometrium, and placenta. A hormone is classically described as a cell product that is secreted into the peripheral circulation and that exerts its effects in distant target tissues (Fig. 15-2). This is termed *endocrine secretion.* Additional forms of cell-cell communication exist and are critical for reproductive physiology. *Paracrine* communication, common within the ovary, refers to chemical signaling between neighboring cells. *Autocrine* communication occurs when a cell releases substances that influence its own function. Production of a substance within a cell that affects that cell before secretion is termed an *intracrine* effect.

FIGURE 15-2

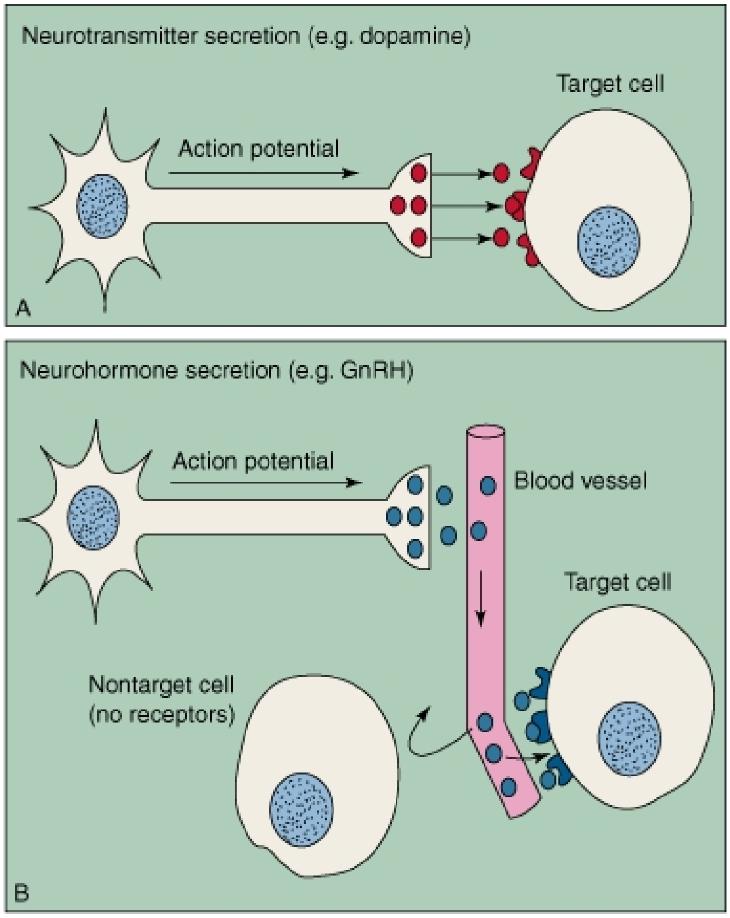


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Drawing displays different types of hormone communication. **A.** Endocrine: hormones travel through the circulation to reach their target cells. **B.** Paracrine: hormones diffuse through the extracellular space to reach their target cells, which are neighboring cells. **C.** Autocrine: hormones feed back on the cell of origin, without entering the circulation.

Neurotransmitters, in classic neural pathways, cross a small extracellular space called a synaptic junction and bind to dendrites of a second neuron (Fig. 15-3). Alternatively, these factors are secreted into the vascular system. They are transported to other tissues where they exert their effects in a process termed *neuroendocrine secretion* or *neuroendocrine signaling.* An example of neuroendocrine signaling is GnRH secretion into the portal vasculature, with effects on nearby tissue. (i.e., the anterior pituitary gland).

FIGURE 15-3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Drawing illustrates types of neurotransmitter secretion. **A.** Classic neurotransmitter release and binding. Transmission of an action potential down a neural axon leads to release of neurotransmitters, which travel across a synaptic cleft to reach their target cell. **B.** Neurohormonal secretion. An action potential leads to release of neurotransmitters. In this instance, neurotransmitters enter into and travel through the circulation to reach their target organ.

REPRODUCTIVE NEUROENDOCRINOLOGY

Neurotransmitters

The list of known neurotransmitters continues to expand as our understanding of their anatomic distribution, mode of regulation, and mechanism of action increases. Neurotransmitters can be classified as: (1) biogenic amines (dopamine, epinephrine, norepinephrine, serotonin, and histamine), (2) neuropeptides, (3) acetylcholine, (4) excitatory amino neurotransmitters (glutamate, glycine, and aspartic acid), (5) the inhibitory amino acid, γ-aminobutyric acid (GABA), (6) gaseous transmitters (nitric oxide and carbon monoxide), and (7) miscellaneous factors (cytokines and growth factors).

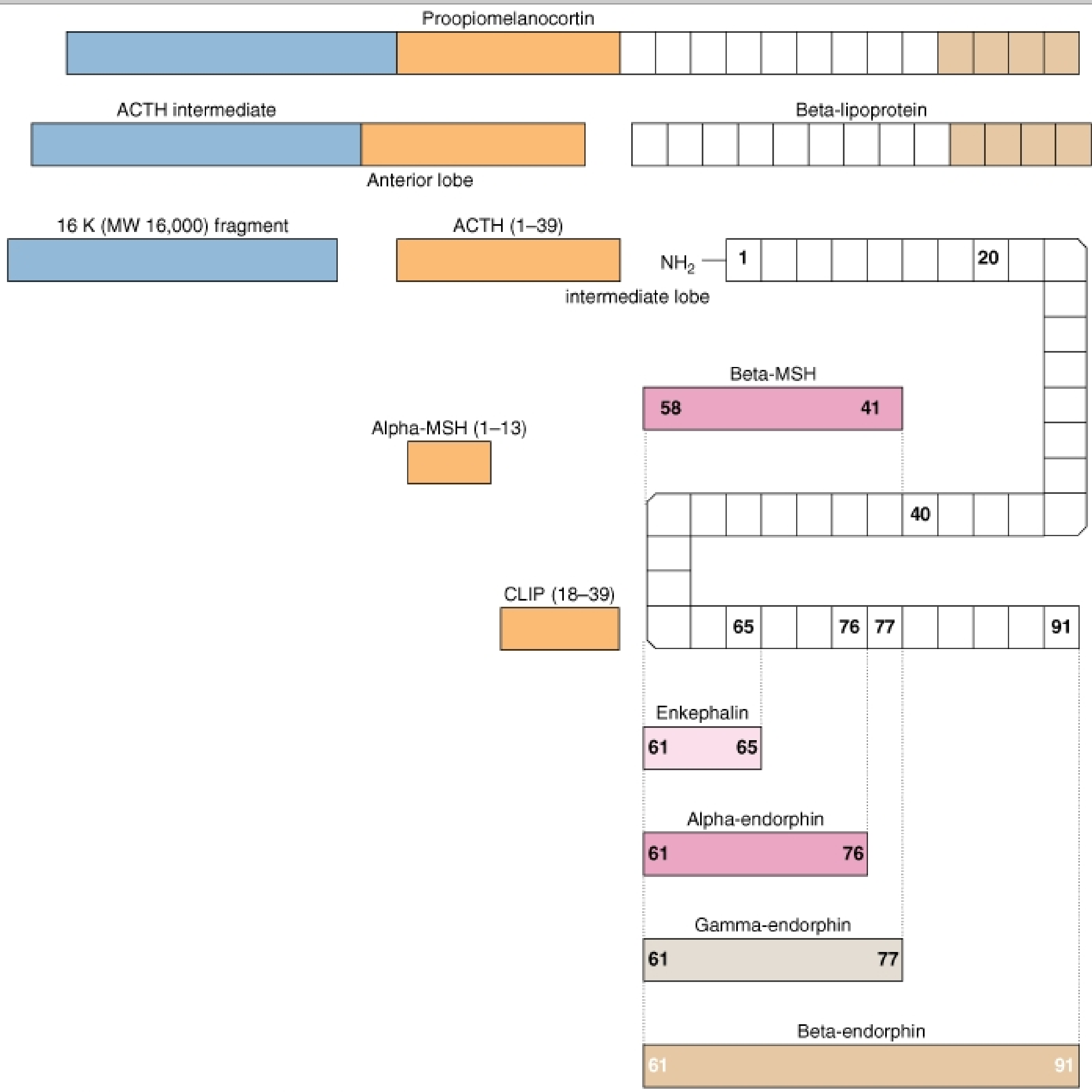
Neuropeptides in Reproduction

More than 50 neuropeptides have been described that influence behavior, pain perception, memory, appetite, thirst, temperature, homeostasis, and sleep. Clinically important neuropeptides include: the endogenous opiates, neuropeptide Y, galanin, and pituitary adenylate cyclaseâ€"activating peptide.

ENDOGENOUS OPIATES

Depending on the precursor peptide from which they are derived, these neuropeptides can be categorized into three classesâ€”endorphins, enkephalins, and dynorphins. Of these, endorphins (endogenous morphines) are cleavage products of the proopiomelanocortin (POMC) gene, which also yields adrenocorticotropin hormone (ACTH) and β-melanocyte stimulating hormone (β-MSH) (Fig. 15-4) (Howlett, 1986; Taylor, 1997). The endorphins serve a wide range of physiologic functions including the regulation of temperature, cardiovascular and respiratory systems, pain perception, mood, and reproduction.

FIGURE 15-4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Proopiomelanocortin (POMC) is a precursor polypeptide from which several biologically important peptides are derived. The site of enzymatic cleavage determines end products. First, POMC is cleaved into an adrenocorticotropin hormone (ACTH) intermediate and β-lipoprotein. The ACTH intermediate is subsequently cleaved to form the mature 39-amino-acid ACTH peptide. In contrast, β-lipoprotein is the source for β-melanocyte stimulating hormone (MSH) and the endogenous opioids, that is, enkephalin, α-endorphin, β-endorphin, and γ-endorphin.
(Redrawn from Speroff, 1999a, with permission.)

Proopiomelanocortin is produced in highest concentration in the anterior pituitary gland, but is also expressed in the brain, sympathetic nervous system, gonads, placenta, gastrointestinal tract, and lungs. The primary peptide synthesized from this pathway depends on the tissue source. For example, the predominant products in the brain are the opiates, whereas pituitary biosynthesis results principally in ACTH production.

Endogenous Opiates' Clinical Effects

Central opioidergic neurons are important mediators of the anterior and posterior pituitary gland. Administration of morphine or its analogues causes release of growth hormone (GH) and prolactin (PRL) and inhibition of gonadotropin and thyroid-stimulating hormone (TSH) release (Grossman, 1983; Houben, 1994). In addition, functional hypothalamic amenorrhea due to eating disorders, intensive exercise, and stress is correlated with an increase in endogenous opiates (see Chap. 16, Functional Disorders or Hypothalamic Amenorrhea). Elevated PRL levels also increase opioid levels in the hypothalamus. This may provide a mechanism, in addition to increased dopamine levels, for the suppression of GnRH pulsatility that occurs with hyperprolactinemia (Khoury, 1987; Petraglia, 1985).

NEUROPEPTIDE Y

The secretion and gene expression of this hypothalamic neuropeptide is highly regulated by gonadal steroids (Sahu, 1992). Neuropeptide Y (NPY) stimulates pulsatile release of GnRH and potentiates the gonadotrope response to GnRH (Pau, 1995). Negative energy balance, as seen with anorexia and bulimia, is associated with an increase in NPY levels. Therefore, it has been proposed that this neuropeptide is at least one link between nutrition and reproductive function (Kaye, 1990; McShane, 1992).

GALANIN

This 29-amino-acid neuropeptide is present in a variety of endocrine glands including the pituitary, pancreas, and adrenal medulla, suggesting that it behaves as a neurohormone. In rat models, galanin is co-expressed in GnRH-containing neurons, and females demonstrate greater levels of galanin than males (Finn, 1996). Its expression in these neurons is induced by estrogen and progesterone. Accordingly, it has been suggested that both NPY and galanin act in concert to modulate pulsatile GnRH release (Xu, 1996).

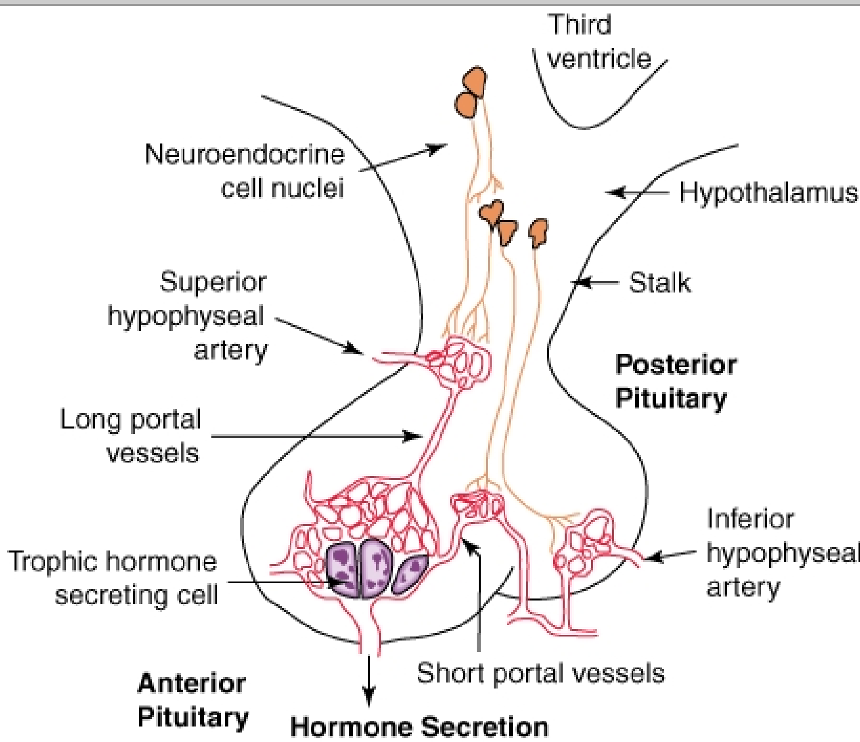
PITUITARY ADENYLATE CYCLASE-ACTIVATING PEPTIDE

Pituitary adenylate cyclaseâ€"activating peptide (PACAP) was first isolated from the hypothalamic arcuate nucleus in sheep (Anderson, 1996). As suggested by its name, PACAP binds to receptors present in the pituitary and stimulates gonadotropin secretion, albeit more weakly than GnRH. It has recently been determined that gonadotropes themselves secrete PACAP, suggesting an autocrine-paracrine role for this hormone. Of interest, PACAP gene expression is greatly increased by GnRH, functionally linking these two important reproductive peptides.

ANATOMY OF THE HYPOTHALAMUS

The hypothalamus is the source of many important neurotransmitters studied in reproductive function, and consists of nuclei located at the base of the brain, just superior to the optic chiasm. Pituitary function is primarily influenced by neurons located within the arcuate, ventromedial, dorsomedial, and paraventricular nuclei (Fig. 15-5).

FIGURE 15-5



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Diagram depicts a sagittal section through the hypothalamus and pituitary gland with rostral structures to the left and caudal ones to the right. The hypothalamus is anatomically and functionally linked with the anterior pituitary by the portal system of blood supply, shown in red. The posterior pituitary consists of axon terminals of magnocellular neurons arising in the supraoptic and paraventricular nuclei of the hypothalamus. *(From Melmed, 2005, with permission.)*

Neurons within the hypothalamus form synaptic connections with other neurons throughout the central nervous system (CNS). In addition, a subset of the hypothalamic neurons project to the median eminence. In the median eminence, a dense network of capillaries arises from the superior hypophyseal arteries. These capillaries drain into portal vessels that traverse the pituitary stalk and then form a capillary network within the anterior pituitary gland (adenohypophysis). The primary direction of this hypophyseal portal system is from hypothalamus to pituitary, however, retrograde flow also exists. This creates an ultrashort feedback loop between the pituitary gland and hypothalamic neurons. The hypothalamus is thus a critical locus for integration of information from the environment, nervous system, and multiple other organ systems.

ANTERIOR PITUITARY GLAND

Initimately connected to the hypothalamus, the pituitary gland contains five hormone-producing cell types: (1) gonadotropes (which produce LH and FSH), (2) lactotropes (PRL), (3) somatotropes (GH), (4) thyrotropes (TSH), and (5) adrenocorticotropes (ACTH). Of these, gonadotropes comprise approximately 10 to 15 percent of all hormonally active cells in the anterior pituitary (Childs, 1983).

With the exception of PRL, which is under tonic inhibition, pituitary hormones are stimulated by hypothalamic neuroendocrine secretion. Although initially felt to be under separate control, it now is known that both of the gonadotropins, LH and FSH, are regulated by a single releasing peptide called gonadotropin-releasing hormone (GnRH) acting on the anterior pituitary's gonadotrope subpopulation. Most gonadotropes contain secretory granules that contain both LH and FSH, although a significant number of cells are monohormonal, that is, secrete either LH or FSH.

Of the other pituitary-releasing hormones, corticotropin-releasing hormone (CRH) stimulates biosynthesis and secretion of ACTH by the pituitary adrenocorticotropes. Thyrotropin-releasing hormone (TRH) increases secretion by the thyrotropes of thyroid-stimulating hormone (TSH), also known as *thyrotropin.* Various hypothalamic secretagogues regulate expression of somatotrope-derived growth hormone (GH). Lastly, PRL expression is primarily under inhibitory regulation by dopamine. As a consequence of these regulatory mechanisms, damage to the pituitary stalk results in hypopituitarism for LH, FSH, GH, ACTH, and TSH, but an associated increase in PRL secretion.

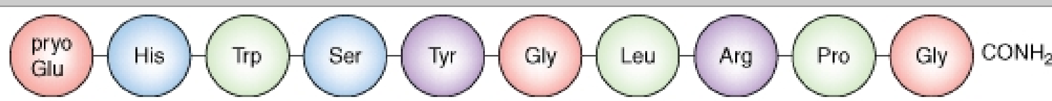
HYPOTHALAMIC-RELEASING PEPTIDES

These peptides have characteristics that are important for both their biologic function and clinical use. First, they are small peptides with short half-lives of a few minutes due to their rapid degradation. Secondly, hypothalamic-releasing peptides are released in minute quantities and are highly diluted in the peripheral circulation. Therefore, biologically active concentrations of these factors are locally restricted to the anterior pituitary gland. Clinically, the extremely low concentrations of these hormones render them essentially undetectable in serum. Thus, levels of their corresponding pituitary factors are measured as surrogate markers.

Gonadotropin-Releasing Hormone

Isolated in the early 1970s, GnRH is a decapeptide with a half-life of less than 10 minutes. Pharmacologic amino acid changes can markedly extend its half-life and change its biologic activity from an agonist to an antagonist (Fig. 15-6). (Redding, 1973).

FIGURE 15-6



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Schematic drawing shows the amino acid composition of the decapeptide gonadotropin-releasing hormone (GnRH).

Most information concerning GnRH and the GnRH receptor are based on studies of a single isoform of each. Recently, however, more than one molecular form of GnRH and their receptors have been identified. With the ability to distinguish between these two receptors, it now appears that the GnRH II receptor is more widely expressed than the classic GnRH I receptor. GnRH II peptide may also have a different expression pattern than GnRH I (Neill, 2002). As a result, significant future work will be required to determine the overlapping and divergent functions of these new proteins.

MIGRATION OF THE GONADOTROPIN-RELEASING HORMONE NEURONS

Whereas other hypothalamic neurons arise within the central nervous system, GnRH-containing neurons have a unique embryologic origin. Specifically, progenitor GnRH neurons originate in the medial olfactory placode and migrate along the vomeronasal nerve into the hypothalamus. A series of soluble factors regulate GnRH neuronal migration at specific locations along their migratory route. These factors include secreted signaling molecules such as GABA, adhesion molecules, and growth factors

(Tobet, 2006; Wierman, 2004). Of these, migration is halted, at least in part, by the 154-amino-acid peptide, kisspeptin. Also known as metastin, this protein is increased at puberty and may provide a link between energy balance and the initiation of puberty.

In primates, GnRH cell bodies are primarily located within the arcuate nucleus. From these neuronal cell bodies, GnRH is axonally transported along the tuberoinfundibular tract to the median eminence. Gonadotropin-releasing hormone (GnRH) is then secreted into the portal system that drains directly to the anterior pituitary gland and stimulates gonadotropin biosynthesis and secretion. The number of GnRH neurons in the adult is strikingly low, and only a few thousand cells are dispersed within the arcuate nucleus.

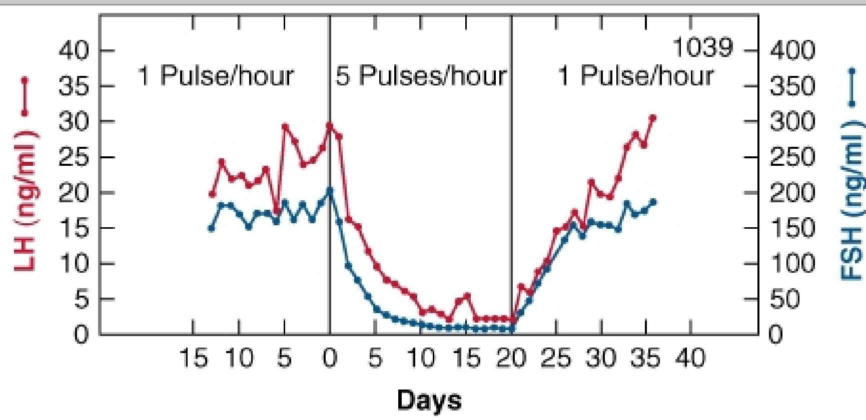
The olfactory origin of GnRH neurons and nasal epithelial cells suggest a link between reproduction and olfactory signals. Compounds released by one individual that affect other members of the same species are known as *pheromones.* Pheromones obtained from the axillary secretions of women in the late follicular phase accelerate the LH surge and shorten the menstrual cycle interval of women exposed to these chemicals. Secretions from women in the luteal phase have the opposite effect. Thus, pheromones may be one mechanism by which women who are together frequently often exhibit synchronous menstrual cycles (Stern, 1998).

A subset of GnRH neurons sends projections into other areas of the central nervous system, including the limbic system. These projections are not required for gonadotropin secretion, but may play a role in modulation of reproductive behavior (Nakai, 1978; Silverman, 1987).

PULSATILE GONADOTROPIN-RELEASING HORMONE SECRETION

In elegant experiments, Ernst Knobil and colleagues demonstrated that pulsatile delivery of GnRH to the pituitary gonadotropes was required to achieve sustained gonadotropin secretion in a primate model (Knobil, 1974). As shown in Fig. 15-7, continuous infusion with GnRH rapidly decreased both LH and FSH secretion, an effect that is easily reversed with a return to pulsatile stimulation. This characteristic is exploited clinically by administration of long-acting GnRH agonists to treat steroid-dependent conditions such as endometriosis, leiomyomas, breast cancer, and prostate cancer. Such agonists disrupt pulsatile GnRH release, lead to depressed gonadotropin secretion, and in turn result in lowered serum ovarian sex steroid levels.

FIGURE 15-7



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Graph shows changes in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels with variation in gonadotropin-releasing hormone (GnRH) pulsatile release. *(Redrawn from Knobil, 1980, with permission.)*

Pulsatile release of GnRH is more frequent but of lower amplitude during the follicular phase compared with that of the luteal phase. More rapid pulse frequencies preferentially stimulate LH, whereas slower frequencies favor FSH secretion (Wildt, 1981). Therefore, changes in GnRH pulse frequency affect both the absolute levels as well as the ratio of LH to FSH release.

Pulsatile activity is currently believed to be an intrinsic property of GnRH neurons. Other hormones and neurotransmitters thus

provide modulatory effects (Clayton, 1981; Yen, 1985). In animal models, estrogen increases GnRH pulse frequency, and therefore leads to an increase in LH levels relative to FSH levels. In contrast, progesterone decreases GnRH pulsatility. As less frequent GnRH pulses preferentially stimulate FSH over LH secretion, the increase in progesterone during the luteal phase may explain the preferential stimulation of FSH observed towards the end of this phase. This rise in FSH is critical for the initiation of follicular recruitment for subsequent cycles.

OPIOID PEPTIDES AND GONADOTROPIN-RELEASING HORMONE

Opioid tone in the brain plays a central role in menstrual cyclicity by suppressing the hypothalamic release of GnRH (Funabashi, 1994). Estrogen promotes endorphin secretion, and this is increased further with the addition of progesterone (Cetel, 1985). Thus, endorphin levels increase during the follicular phase, peak during the luteal phase, and drop markedly during menses. This pattern suggests that opioid tone acts along with progesterone to decrease GnRH pulse frequency in the luteal phase relative to the follicular phase. For reasons that are not fully understood, a release from opioid-suppression of GnRH occurs at the time of ovulation (King, 1984).

For many years, it was thought that GnRH neurons did not express estrogen receptors, and therefore, estrogen feedback at the hypothalamus must occur via effects on hypothalamic neurons with synaptic connections to the GnRH neurons. However, it is now known that GnRH neurons express the estrogen receptor, ER?. Progesterone receptors have not been identified in GnRH-expressing neurons. Therefore, it is currently believed that the ovarian steroids affect GnRH neuronal activity via direct and indirect mechanisms, with opioids acting as a critical intermediary for negative feedback.

OTHER HYPOTHALAMIC-PITUITARY AXES

Dopamine and Prolactin

The most important neurotransmitters in reproductive neuroendocrinology are the three monoaminesâ€”dopamine, norepinephrine, and serotonin. Dopamine-containing fibers that regulate pituitary function arise chiefly in the hypothalamic arcuate nucleus and project to the median eminence where dopamine enters the portal vessels. Dopamine present in hypophyseal-portal vessel blood is of sufficient concentration to inhibit PRL release, and dopamine is the principal prolactin inhibitory factor (PIF) (Table 15-1). In contrast, prolactin-releasing factors, although less potent, include TRH, vasopressin, vasoactive intestinal peptide (VIP), endogenous opioids, and acetylcholine.

Table 15-1 Hypothalamic-Pituitary Products and Their End Organs

Hypothalamus	Pituitary	End Organ
GnRH	LH/FSH	Gonads
Dopamine	PRL	Breast
TRH	TSH	Thyroid
CRH	ACTH	Adrenal
GHRH	GH	Somatic

ACTH = adrenocorticotropin hormone; CRH = corticotropin-releasing hormone; FSH = follicle-stimulating hormone; GH = growth hormone; GHRH = growth hormoneâ€“releasing hormone; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone; PRL = prolactin; TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone.

There are five forms of the dopamine receptor divided into two groups, D_1 and D_2 . Cells in the anterior pituitary gland primarily express the D_2 subtypes. The medical treatment of prolactinomas has been improved in terms of both effectiveness and patient tolerance by the development of the D_2 -specific ligands. For example, the dopamine agonist cabergoline is a D_2 -specific ligand, whereas bromocriptine is nonspecific (Treatment of Pituitary Adenomas).

Thyrotropin-Releasing Hormone

As indicated by its name, thyrotropin-releasing hormone (TRH) stimulates secretion of thyroid-stimulating hormone (TSH) from the anterior pituitary gland's thyrotrope subpopulation. Of note, TRH is also a potent prolactin-releasing factor, and results in a clinical link between hypothyroidism and secondary hyperprolactinemia (see Fig. 16-5) (Krieger, 1980).

Thyroid-stimulating hormone binds to specific receptors on the plasma cell membrane of thyroid cells, stimulating the biosynthesis of thyroid hormones through an increase in thyroid gland size and vascularity. Thyroid hormone exerts negative feedback on TRH and TSH cells.

Corticotropin-Releasing Hormone

This is the primary hypothalamic factor that stimulates synthesis and secretion of ACTH. Consisting of 41 amino acid residues, corticotropin-releasing hormone (CRH) is distributed in multiple locations within the hypothalamus and other CNS areas. Corticotropin-releasing hormone release is stimulated by catecholaminergic input from other brain pathways and inhibited by endogenous opioids.

Corticotropin-releasing hormone binds to a family of CRH receptors and stimulates ACTH biosynthesis and secretion. In turn, ACTH stimulates glucocorticoid production by the adrenal's zona fasciculata and androgen production by its zona reticularis. Corticotropin-releasing hormone secretion is under negative-feedback regulation by circulating cortisol produced in the adrenal gland. In contrast, mineralocorticoid production by the zona glomerulosa is primarily regulated via the renin-angiotensin system. As a result, abnormalities in the CRH-ACTH pathway do not result in electrolyte disturbances.

Central CRH pathways are believed to mediate many stress responses (Sutton, 1982). Clinically, in women with hypothalamic amenorrhea, CRH levels have been found to be elevated. Increased levels of CRH inhibit hypothalamic GnRH secretion by direct action as well as by augmenting central opioid concentrations (see Fig. 16-5). This functional pathway may explain the association between hypercortisolism and menstrual abnormalities.

GROWTH HORMONE-RELEASING HORMONE

Growth hormone secretion by pituitary somatotropes is primarily regulated through stimulation by hypothalamic growth hormoneâ€"releasing hormone (GHRH) and inhibition by somatostatin. Expression of GHRH is limited to the hypothalamus with the exception of placental and immune cells, which also secrete this hormone. In contrast, somatostatin is widely distributed in the CNS as well as in the placenta, pancreas, and gastrointestinal tract.

As with GnRH, GHRH depends on pulsatile secretion to exert a physiologic effect. Exercise, stress, sleep, and hypoglycemia stimulate GH release, whereas free fatty acids and other factors related to adiposity blunt growth hormone release. Estrogen, testosterone, and thyroid hormone also play a role in increased GH secretion.

Growth hormone stimulates skeletal and muscle growth, regulates lipolysis, and promotes the cellular uptake of amino acids. This hormone induces insulin resistance, and therefore, GH excess may be associated with new-onset diabetes mellitus. Most of the GH's growth effects are mediated via the insulin-like growth factors, IGF-I and IGF-II. These growth factors are produced in high quantities in the liver for release into the circulation. Many of the target tissues also synthesize IGFs, where they exert local effects. Within the ovary, IGF-I modulates steroid action during folliculogenesis. This factor also suppresses GH secretion. Circulating IGF-I and IGF-II are bound to binding proteins (IGFBPs), which modulate IGF action at target tissues. In terms of mediating growth factor activity, regulating expression of these binding proteins may be as important as regulation of the IGFs themselves in modulating growth factor activity.

POSTERIOR PITUITARY GLAND

Unlike the anterior pituitary gland, the posterior pituitary (neurohypophysis) consists of the axon terminals of magnocellular neurons from the supraoptic and paraventricular nuclei of the hypothalamus (see Fig. 15-5). These neurons synthesize the nine-amino-acid cyclic peptidesâ€"oxytocin and arginine vasopressin. Precursors for these peptides are produced in the neuronal cell body and transported down the axon in secretory granules. During transport, precursors are cleaved into mature peptides and a carrier proteinâ€"neurophysin (Verbalis, 1983). Activation of these neurons generates an action potential that results in calcium influx and secretion of granule contents into the perivascular space. These secreted peptides then enter adjacent blood vessels for transport throughout the peripheral circulation.

Oxytocin

Oxytocin has significant roles in both parturition and lactation (Kiss, 2005). It is currently believed that this peptide does not play a role in spontaneous initiation of labor, as serum oxytocin levels are constant until the expulsive portion of labor (Fisher, 1983). Nevertheless, an increase in myometrial and decidual oxytocin-receptor expression has been noted near term, primarily due to an increase in estrogen levels.

It is well documented that oxytocin is the primary mediator of myometrial contractility during labor. Cervical and vaginal stimulation results in an acute release of oxytocin from the posterior pituitary in a process known as the *Ferguson reflex* . Clinically, oxytocin's ability to induce uterine contractions is exploited to induce or augment labor.

The anterior pituitary hormone, prolactin, is critical for milk production in breast alveoli. The glandular cells of the alveoli are surrounded by a mesh of myoepithelial cells. Suckling triggers nerve impulses from mechanoreceptors in the nipple and areola that increase hypothalamic neuronal activity. Axon terminals passing to the posterior pituitary gland release oxytocin, which causes the myoepithelial cells to contract and thereby express milk from the alveoli into the ducts and sinuses (Crowley, 1992b). Other conditioned stimuli, such as the sight, sound, or smell of a baby or sexual arousal, will have similar effects. Inhibition of milk let-down can follow stress, fear, embarrassment, or distraction. Therefore, women are encouraged to find a relaxing, private environment when breast feeding.

Oxytocin Expression Outside the Posterior Pituitary

Oxytocin expression has been detected in the anterior pituitary, placenta, fallopian tubes, and gonads, with high expression in the corpus luteum (Williams, 1990). Vaginal distension, such as that which occurs with coitus, also increases oxytocin release. Based on this observation, it has been suggested that oxytocin may be responsible for the rhythmic uterine and tubal contractions that aid in sperm delivery to the oocyte. Oxytocin may also play a role in orgasm and ejaculation.

CLINICAL HYPOTHALAMIC-PITUITARY AXIS ABNORMALITIES

Kallmann Syndrome

This syndrome is a developmental disorder characterized by the inability to smell (anosmia) and hypogonadotropic hypogonadism. Anosmia likely results from abnormal migration of olfactory neurons. Concurrent failure of appropriate GnRH neuronal migration leads to absent stimulation of gonadotropin biosynthesis and secretion (Crowley, 1992a). The pathophysiology and characteristics of this syndrome are further discussed in Chapter 16, Hypogonadotropic Hypogonadism.

Panhypopituitarism

This total loss of anterior pituitary function may develop following surgical or radiation treatment of pituitary adenomas. Panhypopituitarism following severe postpartum hemorrhage and the resultant hypotension is called *Sheehan syndrome.* Sheehan syndrome is relatively uncommon in industrialized nations due to resources for adequate intrapartum blood volume resuscitation. As would be expected, Sheehan syndrome is more commonly found in countries with developing health care systems. Patients exhibit characteristic clinical manifestations including failure to lactate or ovulate, loss of sexual and axillary hair, hypothyroidism, and adrenal insufficiency. Development of symptoms typically follows this order, although loss of function of the various pituitary cell types may not be complete in all women.

Hyperprolactinemia

ETIOLOGY OF HYPERPROLACTINEMIA

Elevated circulating prolactin levels can be caused by a variety of physiologic activities including pregnancy, sleep, eating, and coitus. Increased prolactin levels may also be observed following chest wall stimulation such as that which occurs with suckling, breast examination, chest wall surgery, herpes zoster infection, or nipple piercing (see Table 12-3). Prolactin is primarily regulated by tonic dopamine inhibition of secretion. Prolactin secretion is increased by serotonin, norepinephrine, opioids, estrogen, and TRH. Therefore, medications that block dopamine receptor action (phenothiazines) or deplete catecholamine levels (monoamine oxidase inhibitors [MAOIs]) may increase PRL levels (see Table 12-4). Moreover, hyperprolactinemia may be caused by tumor, radiation, or infiltrative diseases such as sarcoid and tuberculosis, which damage the pituitary stalk and prevent dopamine-mediated inhibition of PRL secretion (see Table 12-3).

Primary hypothyroidism is also associated with mild elevations in serum PRL levels (Van Gaal, 1981). Low circulating thyroid hormone levels produce a reflex increase in hypothalamic TRH levels due to loss of feedback inhibition. Thyrotropin-releasing hormone can bind directly to anterior pituitary lactotropes and stimulate PRL production (Haisenleder, 1992). As a rule, thyroid function tests should be measured when confirming a diagnosis of hyperprolactinemia, as a patient may require thyroid replacement rather than further evaluation for pituitary adenoma.

Prolactin-secreting adenomas, also termed prolactinomas, are the most common pituitary adenoma and the most common adenomas to be diagnosed by gynecologists. Most affected women present with microadenomas and signs of PRL excess such as galactorrhea and amenorrhea (Davis, 2004).

DIAGNOSIS OF HYPERPROLACTINEMIA

Serum Prolactin Levels

Hyperprolactinemia is, by definition, present in any patient with an elevated serum PRL level. Optimally, PRL levels are drawn in the morning, that is, at the time of the PRL nadir. Prior to testing, breast examination is avoided to prevent false-positive results. If a mildly elevated PRL level is found, sampling should be repeated because PRL levels vary throughout the day. Moreover, many factors including the stress of venipuncture may produce false elevations.

Normal PRL levels are typically less than 20 ng/mL in nonpregnant women, although the upper limit of normal varies by assay. Importantly, PRL levels rise nearly 10-fold during pregnancy and make detection of a prolactinoma difficult at this time. Occasionally the reported prolactin value will be falsely low due to a "hook effect" present in the assay (Frieze, 2002). That is, in the presence of very high levels of endogenous hormone, oversaturation of test antibodies prevents required competition between a patient's PRL and the labeled assay PRL. This problem is overcome with dilution of a patient's sample. Importantly, a mismatch between the adenoma size noted on magnetic resonance (MR) imaging and the degree of PRL level elevation should alert a clinician to the possibility of either an incorrect assay result or the likelihood that the macroadenoma is actually not primarily PRL secreting. Macroadenomas of any cell type may damage the pituitary stalk and prevent transfer of hypothalamic dopamine to the lactotropes.

Conversely, a patient may rarely have an elevated PRL level on assay despite a lack of clinical features of hyperprolactinemia. The hyperprolactinemia in these patients is thought to be secondary to alternate forms of PRL, including the so-called "big" or macroprolactin, which contains multimers of native PRL. Macroprolactin is not physiologically active, but may be detected by PRL assays (Fahie-Wilson, 2005).

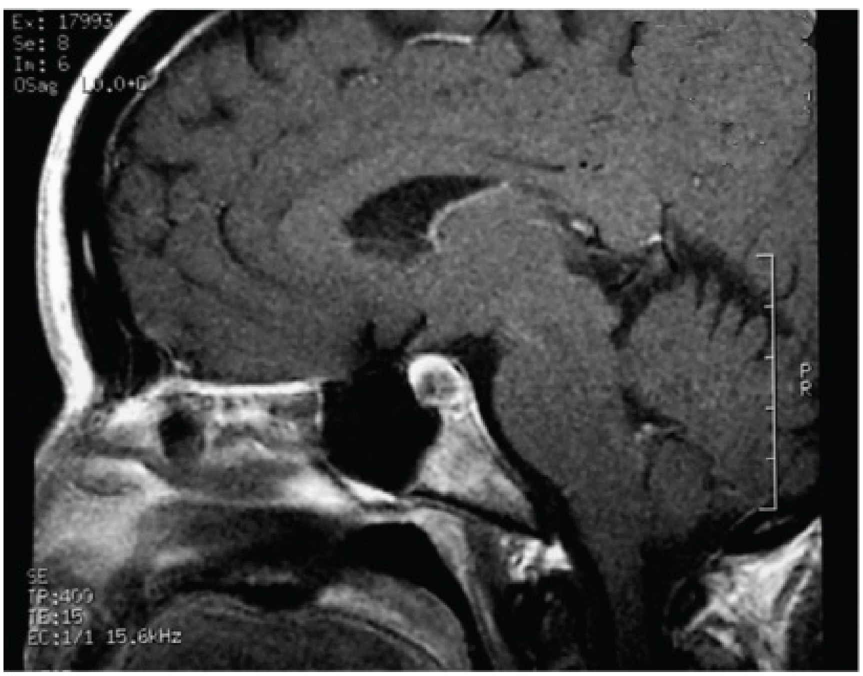
Radiologic Imaging

Magnetic resonance imaging is advisable for all patients with confirmed hyperprolactinemia. Some experts advocate limiting imaging to women with a PRL level exceeding 100 ng/mL, as lower levels are most likely due to small microadenomas (Fig. 15-8). Although this is undoubtedly a safe approach in most women, mildly elevated PRL levels also may be due to pituitary stalk compression by a non-prolactin-secreting macroadenoma or a craniopharyngioma, which are diagnoses with potentially severe consequences.

FIGURE 15-8

A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Magnetic resonance image of a pituitary microadenoma (**arrows**). **A.** Coronal image. **B.** Sagittal image.

TREATMENT OF HYPERPROLACTINEMIA

Treatment of hyperprolactinemia should begin with treatment of the underlying cause. For example, medications should be changed, if possible, or hypothyroidism should be treated. The management of pituitary adenomas includes dopamine agonists, such as bromocriptine (see Treatment of Pituitary Adenomas). Bromocriptine therapy can be reasonable instituted in a woman with a mildly elevated prolactin level and a normal pituitary on imaging. These patients can be presumed to have a small microadenoma, although the incidence of this presentation is decreasing with the advent of highly sensitive MR imaging.

Pituitary Adenomas

CLASSIFICATION OF ADENOMAS

Pituitary adenomas are the most common cause of acquired pituitary dysfunction and comprise approximately 10 percent of all intracranial tumors. Clinically, symptoms of galactorrhea, menstrual disturbances, or infertility may lead to its diagnosis. Most tumors are benign, with only an estimated 0.1 percent of adenomas developing into frank carcinoma with metastasis (Kaltsas, 2005). Nevertheless, pituitary adenomas may cause striking abnormalities in both endocrine and nervous system function (Table 15-2).

Table 15-2 Clinical Features of Pituitary Adenomas

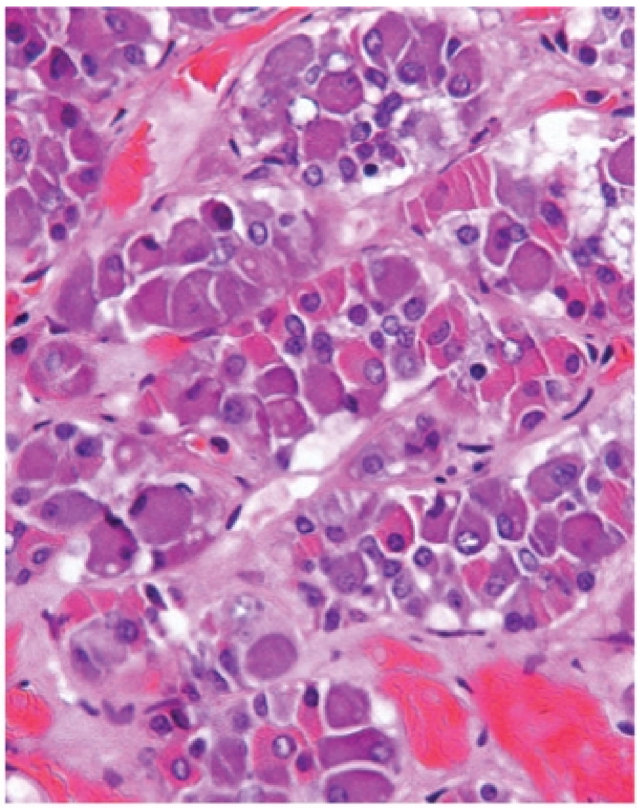
Adenomas Cell Origin	Hormone Product	Clinical Syndrome	Reproductive Effects	Testing	Typical Results	Treatment
Lactotrope	PRL	Hypogonadism, galactorrhea	Disrupts GnRH pulsatility	Serum PRL level	Elevated	Surgical excision; dopamine agonist;see Fig. 15-10
Gonadotrope	subunits FSH, LH, subunits	Silent or hypogonadism; less commonly, gonadotropin excess or panhypopituitarism	Disrupts GnRH pulsatility	Serum gonadotropin α -subunit	Elevated	Surgical excision
Somatotrope	GH	Acromegaly/gigantism, menstrual irregularity	Disrupts GnRH pulsatility, ovarian steroidogenesis, LH receptor synthesis, and inhibin secretion	IGF-I level, 100-g glucose suppression test	Elevated No GH suppression	Surgical excision; somatostatin agonists:a octreaotide or lanreotide
Corticotrope	ACTH	Cushing syndrome, amenorrhea	Disrupts GnRH pulsatility	24-hr urine collection with free cortisol measurement	Elevated serum ACTH and urinary cortisol levels	Surgical excision; ketoconazole blunts adrenal steroidogenesis
				CRH stimulation test	Elevated serum ACTH and cortisol levels	
				BIPSS	ACTH levels in BIPSS sample higher than in serum	

Thyrotrope	TSH	Thyrotoxicosis, menstrual abnormalities	Increases SHBG; Increases conversion of androgens to estrogens	Serum TSH, T_3, and T_4 levels	All elevated	Surgical excision, PTU or tapazole preoperatively to normalize thyroid levels, β-blockers to control associated tachycardia

ACTH = adrenocorticotropin hormone; BIPSS = bilateral inferior petrosal sinus sampling; CRH = corticotropin-releasing hormone; FSH = follicle-stimulating hormone; GH = growth hormone; GnRH = gonadotropin-releasing hormone; IGF = insulin-like growth factor; LH = luteinizing hormone; PRL = prolactin; PTU = propylthiouracil; SHBG = sex-hormone binding globulin; TSH = thyroid-stimulating hormone. T_3 = triiodothyronine; T_4 = thyroxine.

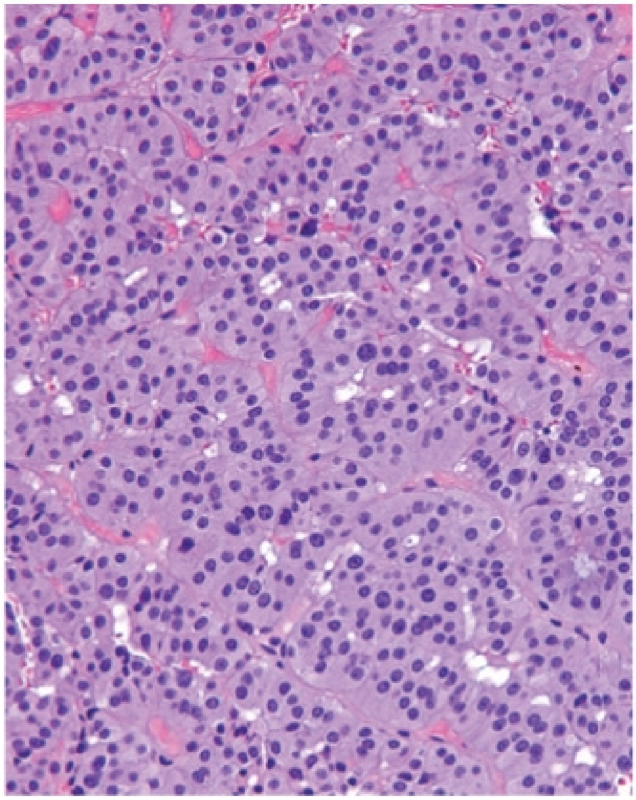
Pituitary adenomas were historically classified as eosinophilic, basophilic, or chromophobic, according to their hematoxylin and eosin staining characteristics. Tumors are now classified by their hormonal expression pattern as determined by immunohistochemistry (Fig. 15-9). Adenomas are further grouped by size into microadenomas (<10 mm in diameter) and macroadenomas (>10 mm in diameter).

FIGURE 15-9



A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



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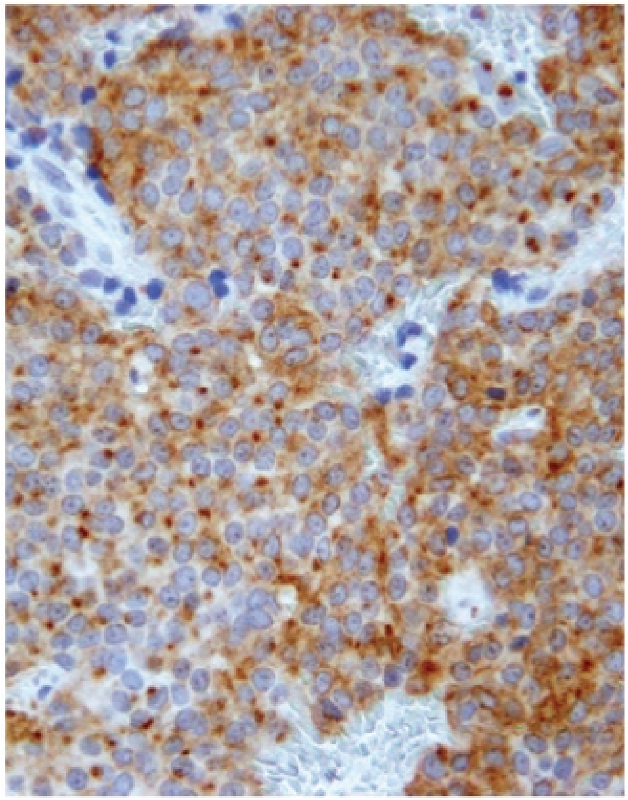
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



C

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photomicrographs from the anterior pituitary gland. **A.** Normal anterior pituitary gland. Secretory cells of the various types are arranged in small clusters between sinusoidal capillaries. (H&E, 200x). **B.** Pituitary adenoma. In contrast to normal anterior pituitary gland, adenomas are composed of highly monomorphic cells. Note the absence of small clusters and sinusoids. (H&E, 100x). **C.** Prolactin-secreting adenoma. Immunohistochemistry demonstrates expression of prolactin by many of the neoplastic cells. The dot-like pattern is characteristic of many prolactin-producing adenomas. (HRP/DAB, 100x). *(Courtesy of Dr. Jack Raisanen.)*

Most adenomas secrete PRL, however, adenomas may secrete any of the pituitary hormones either as a single hormone (monohormonal adenoma) or in combinations (multihormonal adenoma). In the past, a subset of tumors was considered nonsecreting. However, with more sensitive assays, most have been determined to secrete the common α-subunit or the gonadotropin β-subunits, and thus are gonadotrope-derived (Luteinizing Hormone, Follicle-Stimulating Hormone, and Human Chorionic Gonadotropin). Rarely, both α- and β-subunits are secreted as functional dimeric hormone.

PITUITARY ADENOMA SYMPTOMS

Endocrinopathy

Pituitary adenomas may cause symptoms via excess hormone secretion and lead to clinical conditions such as hyperprolactinemia, acromegaly, or Cushing disease. Alternatively, adenomas may result in hormone deficiency due to damage of other pituitary cell types or of the pituitary stalk by an expanding adenoma or following treatment of the primary lesion.

As might be predicted, pituitary microadenomas are typically diagnosed during evaluation of an endocrinopathy, whereas macroadenomas frequently come to medical attention when a patient presents with symptoms from invasion of surrounding structures. The anterior pituitary gland borders both the optic chiasm and cavernous sinus. Disruption of the optic chiasm by suprasellar growth of the pituitary mass may present as bitemporal hemianopsia in which patients lose of the outer portion of the

right and left visual fields. Cavernous sinus syndrome consists of a constellation of symptoms including headache, visual disturbances, and cranial nerve palsies, specifically cranial nerves III, IV, and VI.

Pituitary Apoplexy

Spontaneous hemorrhage into a pituitary adenoma, termed *pituitary apoplexy,* is a rare life-threatening medical emergency. Apoplexy may lead to severe hypoglycemia, hypotension, CNS hemorrhage, and death. Signs and symptoms include acute visual changes, severe headache, neck stiffness, hypotension, loss of consciousness, and coma. These symptoms result from: (1) leakage of blood and necrotic material into the subarachnoid space, (2) acute hypopituitarism, and (3) development of a rapidly expanding hemorrhagic intrasellar mass that compresses the optic chiasm, cranial nerves, hypothalamus, and/or internal carotid arteries.

Reproductive Effects

Any pituitary mass or infiltrate can present as an abnormality in reproductive function that may include delayed puberty, anovulation, oligomenorrhea, and infertility. The exact mechanisms linking adenomas to menstrual dysfunction are not well understood for many adenoma subtypes, perhaps with the exception of prolactinoma. Hyperprolactinemia results in a reflex increase in central dopamine. Stimulation of the dopaminergic receptors on the GnRH neurons alters GnRH pulsatility, thereby disrupting folliculogenesis. It has been postulated that non-prolactin-secreting adenomas may affect reproductive function either by compressing the pituitary stalk with resultant hyperprolactinemia or by directly compressing gonadotropes. Additional mechanisms undoubtedly exist in view of the complexity of the interactions between the various hormones, peptides, and neurotransmitters that influence hypothalamic function.

PITUITARY ADENOMA DIAGNOSIS

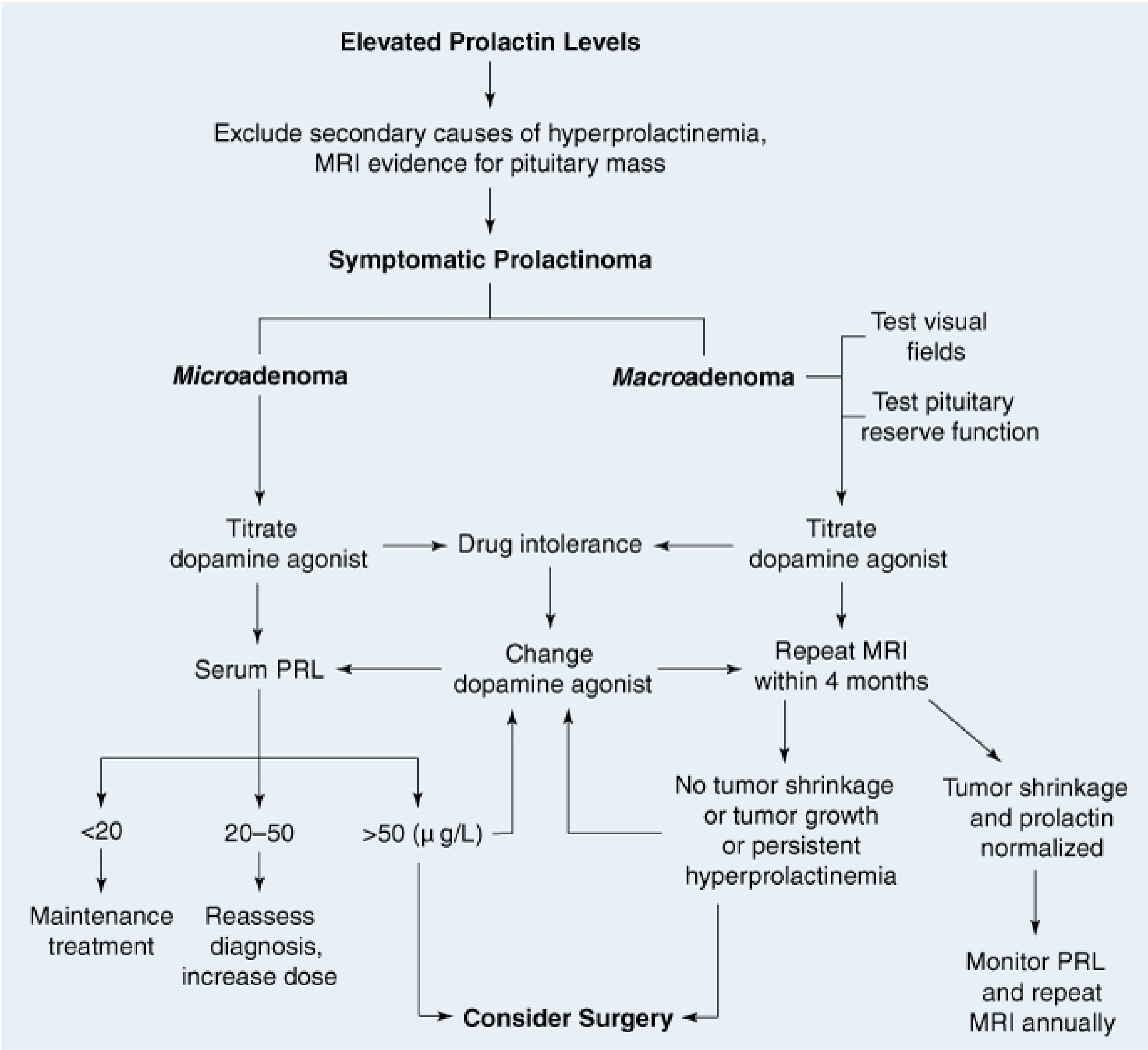
The availability of sensitive neuroimaging techniques now affords earlier diagnosis and intervention. In the past, pituitary adenomas were identified using a coned-down view of the sella turcica during standard head radiography. Although computed tomographic (CT) scanning provides useful information on tumor size, bony artifacts may limit interpretation. Therefore magnetic resonance (MR) imaging, using both T1- and T2-weighted images, has become the primary radiologic method due to its high sensitivity and excellent spatial resolution (Ruscalleda, 2005). Frequently, MR imaging is performed with and without gadolinium infusion for maximum definition of tumor size and extension.

TREATMENT OF PITUITARY ADENOMAS

Specifically, for those with prolactin-secreting adenomas, most tumors grow slowly, and many cease growth after attainment of a certain size. Thus, asymptomatic patients with a microprolactinoma may be managed conservatively with serial MR imaging and serum PRL levels every 1 to 2 years, as the risk of progression to a macroadenoma is less than 10 percent (Schlechte, 1989). These women should be followed for even mild changes in menstrual cyclicity, as they are at risk for developing hypoestrogenism and resultant risk for osteopenia or osteoporosis (Klibanski, 1980).

When tumors of any size are associated with symptoms of amenorrhea or galactorrhea, therapy should be considered (Fig. 15-10). Neurosurgical evaluation is mandatory when visual field defects or severe headaches are present. In general, first-line treatment is medical for both micro- and macroadenomas. Specifically, women should receive a dopamine agonist such as the nonspecific dopamine receptor agonist, bromocriptine (Parlodel, Novartis, Novartis Pharmaceuticals, East Hanover, NJ), or the dopamine receptor type 2 agonist, cabergoline (Dostinex, Pfizer, New York, NY).

FIGURE 15-10



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Algorithm describing the evaluation and treatment of pituitary adenomas. MRI = magnetic resonance imaging; PRL = prolactin. *(Redrawn from Melmed, 2005, with permission.)*

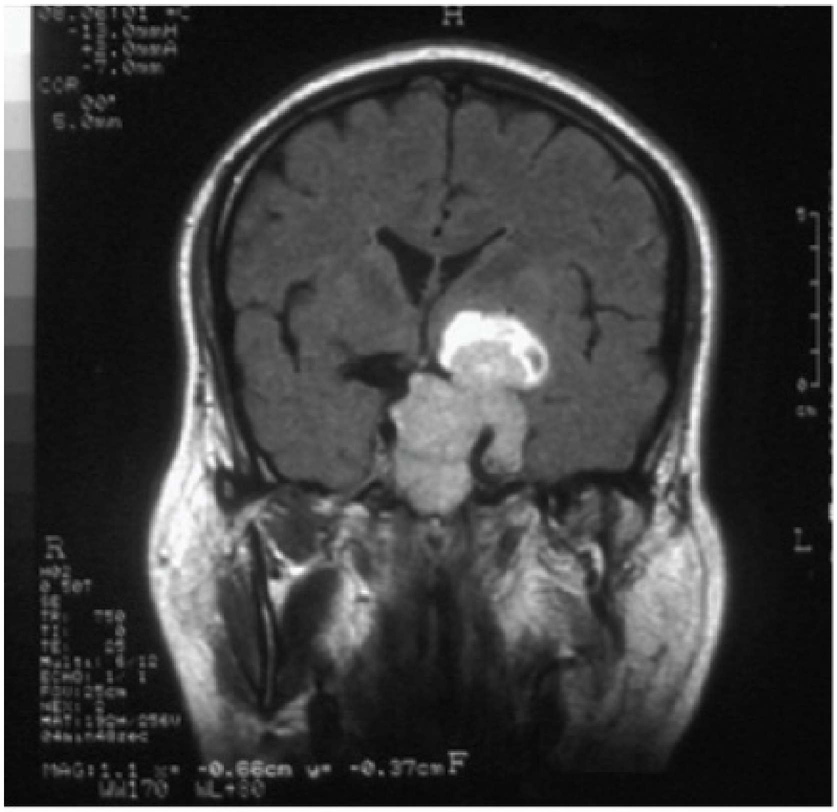
These dopamine agonists decrease PRL secretion and shrink tumor size (Molitch, 2001). However, bromocriptine treatment is associated with a number of common side effects including headache, postural hypotension, blurred vision, drowsiness, and leg cramps. Most of these are attributable to activation of type 1 dopamine receptors. Due to its receptor specificity, cabergoline treatment is generally better tolerated than bromocriptine. Cabergoline also has a longer half-life than bromocriptine, allowing once- or twice-weekly dosing compared with the multiple daily doses that may be required for bromocriptine. Typical initial cabergoline dosages are 0.25 mg orally daily twice weekly. Cabergoline has been found to be more effective than bromocriptine in normalizing PRL levels (Di Sarno, 2001; Webster, 1994). Nevertheless, cabergoline can be prohibitively expensive. Most patients

can tolerate bromocriptine if started at a low doseâ€”Â½ tablet or 0.125 mgâ€”each night to minimize associated nausea and dizziness. This dose can be slowly increased to three times daily as tolerated. Reliable measurement of posttreatment serum prolactin levels can be obtained 1 month following a steady medication dose.

Surgery

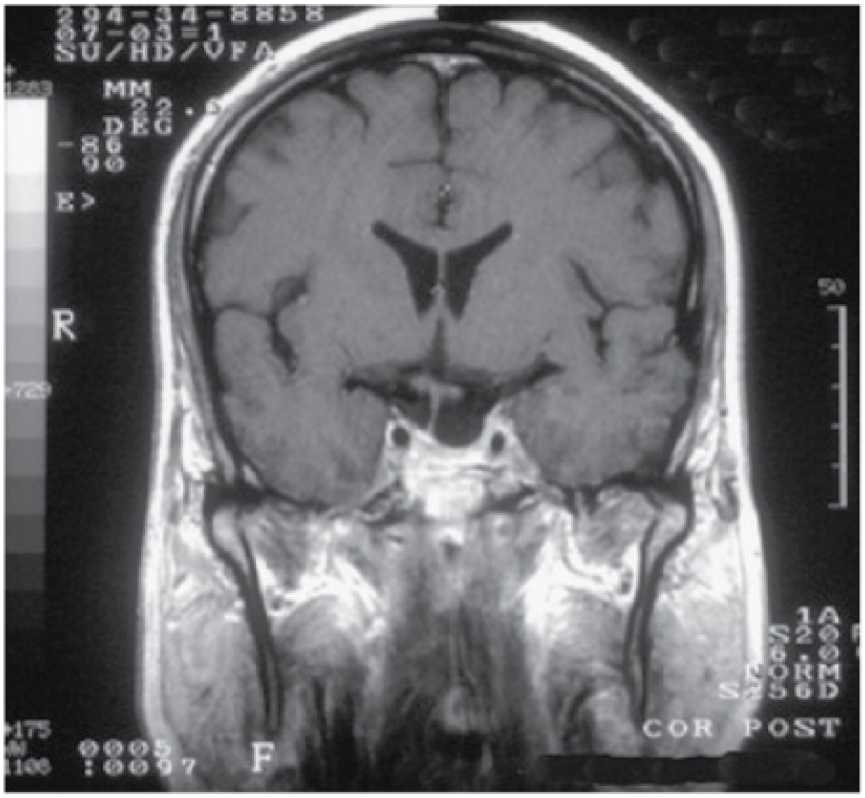
Neurosurgery is required for refractory tumors or those causing acutely worsening symptoms. The pituitary is approached through a transsphenoidal route whenever possible (Fig. 15-11). Complications of surgery, although rare, include intraoperative hemorrhage, a cerebrospinal fluid leak (rhinorrhea), diabetes insipidus, damage to other pituitary cell types, and meningitis (Arafah, 1986; Molitch, 1999). Radiation therapy may be used for patients with surgically nonresectable or persistent tumors.

FIGURE 15-11



A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Magnetic resonance image of a pituitary before and after surgical resection of a macroadenoma. **A.** Preoperative coronal image reveals tumor measuring greater than 10 mm. **B.** Postoperative coronal image of the same patient following tumor excision.

Other Treatments

Depending on the success of these approaches, additional therapies such as radiation therapy may be required to manage residual symptoms. The gamma knife allows precise focus of the radiation beam, significantly decreasing adjacent tissue damage and improving patient tolerance.

Gene therapy has been proposed as a treatment for pituitary tumors. Possibilities include the introduction of genes that encode growth-inhibiting factors by retroviral infection. Additional studies are needed to determine whether this approach will be safe and efficacious (Seilicovich, 2005).

PREGNANCY AND PITUITARY ADENOMAS

The pituitary gland enlarges during pregnancy, primarily due to hypertrophy and hyperplasia of the lactotropes in response to elevated serum estrogen levels. Although there is a risk of tumor enlargement during pregnancy, clinical experience has shown that the risk is small, particularly for microadenomas (Molitch, 1985, 1999). However, because significant expansion may lead to headaches or compression of the optic chiasm and blindness, visual field testing should be considered every trimester for women with macroadenomas. Although it is likely to be safe, most experts advise that dopamine agonist therapy be discontinued during pregnancy (Webster, 1996).

HORMONE BIOSYNTHESIS AND MECHANISM OF ACTION

Hormones can be broadly classified as either steroids or peptides, each with their own mode of biosynthesis and mechanism of

action. These hormones' receptors can be divided into two groups: (1) those present on the cell surface, which in general interact with hormones that are water soluble, namely peptides, and (2) those that are primarily intracellular and interact with lipophilic hormones such as steroids. Hormones are normally present in serum and tissues in very low concentrations. Therefore, receptors must have both high affinity and high specificity for their ligand to produce the correct biologic response.

Peptide Hormones in Reproduction

LUTEINIZING HORMONE, FOLLICLE-STIMULATING HORMONE, AND HUMAN CHORIONIC GONADOTROPIN

Structurally, LH and FSH are heterodimers that contain a common α-subunit linked to either the LHβ or FSHβ subunit, respectively. The common glycoprotein α-subunit also interacts with the thyrotropin-stimulating hormone β-subunit to form TSH, and with the human chorionic gonadotropin β-subunit to form hCG. The similarity of these hormones can have clinical sequelae. For example, molar pregnancies frequently produce very high levels of hCG, which can bind to TSH receptors, producing hyperthyroidism. Importantly, only the dimers possess biologic activity. Although the subunits can be found in their unassociated form in the circulation, these "free" subunits are not known to have physiologic significance.

The LH and hCG β-subunits are encoded by two separate genes within a gene grouping called the LH/CG cluster. The amino acid sequence of the human LH and CG β-subunits demonstrates approximately 80 percent similarity. However, the hCG β-subunit contains an additional 24-amino-acid extension on the carboxy terminus. The presence of these additional amino acids has allowed the development of highly specific assays for both LH and hCG.

ACTIVIN, INHIBIN, AND FOLLISTATIN

Three polypeptide factorsâ€”*inhibin, activin,* and *follistatin* â€”were initially isolated from follicular fluid and named based on their selective effects on FSH biosynthesis and secretion (Halvorson, 1996). Inhibin decreases and activin stimulates gonadotrope function. Follistatin suppresses FSHβ gene expression, most likely by binding to and thereby preventing the interaction of activin with its receptor (Besecke, 1997; Kogawa, 1991). Subsequent studies have indicated that these peptides also affect biosynthesis of LH and the GnRH receptor, although these responses are less robust (Kaiser, 1997).

Inhibin and activin are closely related peptides. Inhibin consists of an α-subunit (unrelated to the LH glycoprotein α-subunit) linked by a disulfide bridge to one of two highly homologous β-subunits to form inhibin A ($\alpha\beta_A$) or inhibin B ($\alpha\beta_B$). Activin is composed of homodimers ($\beta_A\ \beta_A$, $\beta_B\ \beta_B$) or heterodimers ($\beta_A\ \beta_B$) of the same β-subunits as inhibin (Dye, 1992; Halvorson, 1996). More recently, a number of additional β-subunit isoforms have been identified. In contrast, follistatin is structurally unrelated to either inhibin or activin.

Although originally isolated from follicular fluid, these "gonadal" peptides are expressed by a wide variety of reproductive tissues in which they provide diverse, tissue-specific functions (Meunier, 1988). The mRNAs that encode the inhibin/activin subunits, follistatin, and the activin receptor have been detected in the pituitary, ovary, testes, and placenta, as well as in the brain, adrenal, liver, kidney, and bone marrow (Kaiser, 1992).

Of these peptides, inhibin is currently believed to be most critical for the feedback regulation of gonadotropin gene expression. In contrast, activin and follistatin effects on gonadotrope function most likely occur through the action of locally released peptides acting as autocrine/paracrine factors.

Steroid Hormones in Reproduction

BIOSYNTHESIS AND METABOLISM

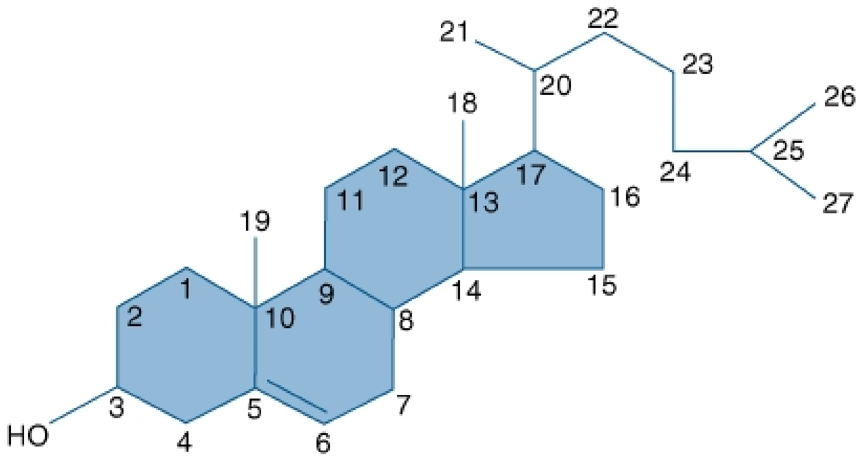
Sex steroid hormones are synthesized in the gonads, adrenal gland, and placenta. Cholesterol is the primary building block in steroidogenesis, and all steroid-producing tissues except the placenta are capable of synthesizing cholesterol from the 2-carbon precursor, acetate. Steroid hormone production, which involves at least 17 enzymes, primarily occurs in the abundant smooth endoplasmic reticulum found in steroidogenic cells (Mason, 2002).

Steroids are metabolized mainly in the liver and to a lesser extent in the kidney and intestinal mucosa. Accordingly, administration of certain pharmacologic steroid hormones may be contraindicated in those with active liver disease.

STEROID HORMONE CLASSIFICATION

Sex steroids are divided into three groups based on the number of carbon atoms that they contain. Each carbon in this structure is assigned a number identifier, and each ring is assigned a letter (Fig. 15-12). The 21-carbon series includes progestins as well as glucocorticoids and mineralocorticoids. Androgens contain 19 carbons, whereas estrogens have 18.

FIGURE 15-12



Cholesterol

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Diagram displays the chemical structure of cholesterol, which is the common precursor in sex steroid biosynthesis. All sex steroids contain the basic cyclopentanephenanthrene molecule, which consists of three 6-carbon rings and one 5-carbon ring. *(From Carr, 2005b, with permission.)*

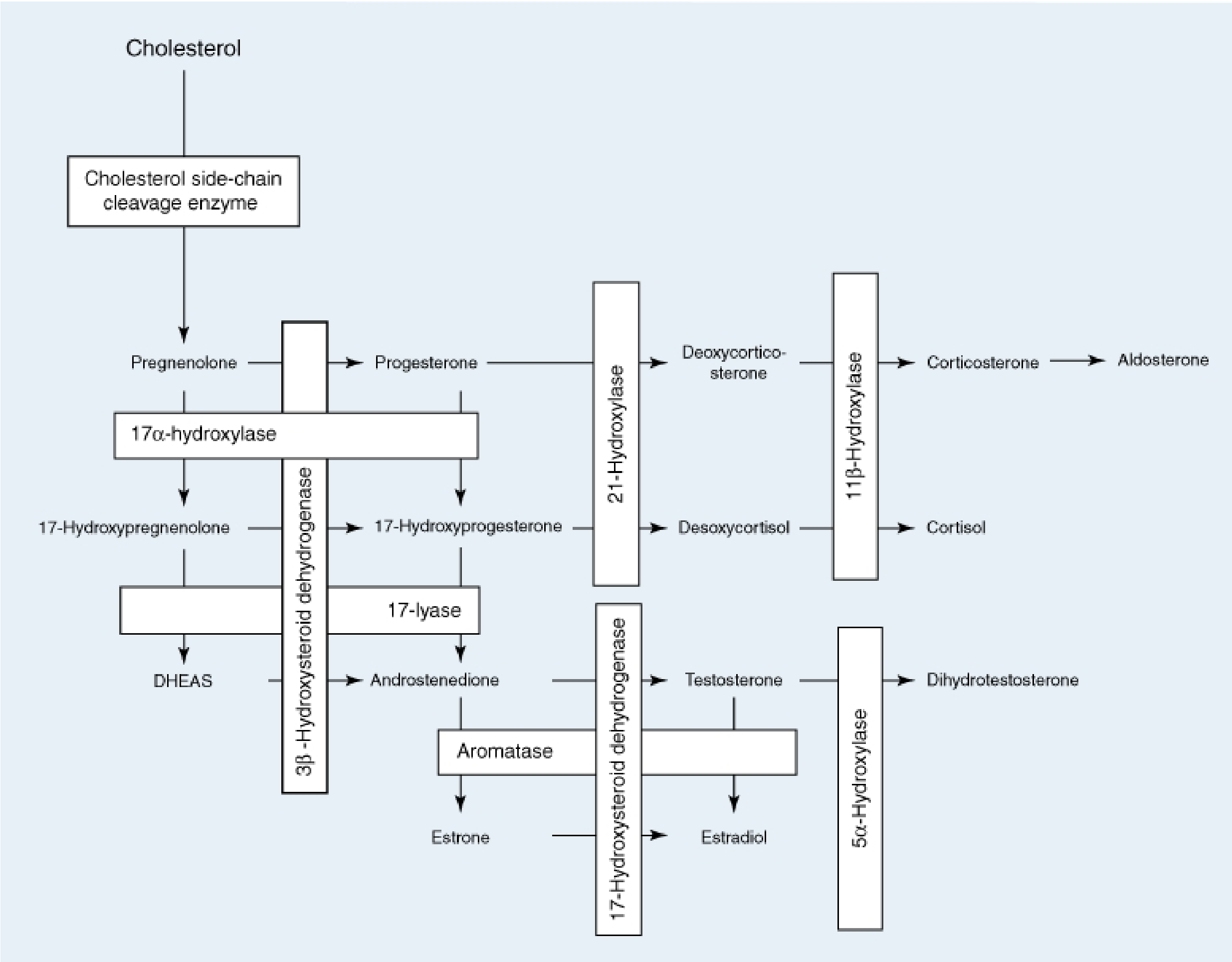
Steroids are accorded scientific names according to a generally accepted convention in which functional groups below the plane of the molecule are preceded by the α symbol and those above the plane of the molecule are indicated by a β symbol. A Δ symbol indicates a double bond. Those steroids with a double bond between carbon atoms 5 and 6 are called Δ^5 steroids (pregnenolone, 17-hydroxypregnenolone, and dehydroepiandrosterone). Those with a double bond between carbons 4 and 5 are termed Δ^4 steroids (progesterone, 17-hydroxyprogesterone, androstenedione, testosterone, mineralocorticoids, and glucocorticoids).

Steroidogenic enzymes catalyze four basic modifications of the steroid structure: (1) side-chain cleavage (desmolase reaction), (2) conversion of hydroxyl groups to ketones (dehydrogenase reactions), (3) addition of a hydroxyl group (hydroxylation reaction), and (4) removal or addition of hydrogen to create or reduce a double bond (Table 15-3). The steroid biosynthesis pathway is shown in simplified form in Fig. 15-13. The distribution of products synthesized by each tissue is determined by the presence of requisite enzymes. For example, the ovary is deficient in 21-hydroxylase and 11β-hydroxylase and therefore is unable to produce corticosteroids.

Table 15-3 Steroidogenic Enzymes

Enzyme	Cellular Location	Reactions
P450scc	Mitochondria	Cholesterol side chain cleavage
P450c11	Mitochondria	11-Hydroxylase
		18-Hydroxylase
		19-Methyloxidase
P450c17	Endoplasmic reticulum	17-Hydroxylase
		17, 20-Lyase
P450c21	Endoplasmic reticulum	21-Hydroxylase
P450arom	Endoplasmic reticulum	Aromatase

FIGURE 15-13



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Diagram depicts steps in the steroidogenesis pathway. DHEAS = dehydroepiandrosterone. *(From Timmreck, 2005, with permission.)*

CLINICAL EFFECT OF CERTAIN STEROIDOGENIC STEPS

Congenital Adrenal Hyperplasia

Typically due to a 21-hydroxylase deficiency, classic congenital adrenal hyperplasia (CAH) is one of the most common autosomal recessive metabolic diseases, estimated to occur in 1:10,000 to 1:15,000 births. Although CAH has been reported in a wide range of ethnic groups, it is most common in the Ashkenazi Jewish population. Alternatively, deficiencies in 11β-hydroxylase activity account for 5 to 8 percent of CAH cases.

Patients with CAH exhibit a broad range of clinical phenotypes depending on the extent of enzymatic deficiency. On one extreme, gene conversions and large deletions lead to severe enzyme deficiency and present as salt-wasting CAH in the neonate. Moreover, in this form of CAH, a block at the 21-hydroxylase step results in markedly reduced levels of aldosterone and cortisol. The back-up of precursors shifts steroidogenesis towards the androgen pathway. Therefore, females with CAH may present with female pseudohermaphroditism (female karyotype with masculinized external genitalia) (see Chap. 18, Congenital Ambiguity of the Genital Tract). Unless replaced with corticosteroids, these neonates will die shortly after birth. A less severe mutation may lead to simple virilizing CAH. As its name suggests, this condition is notable for sufficient corticosteroid production but increased androgen levels.

In a nonclassic form of CAH, also known as late-onset or adult-onset CAH, hyperandrogenemia does not present until puberty. The incidence of nonclassic disease has been estimated at 1:1,000 births. At puberty, activation of the adrenal axis increases

steroidogenesis, unmasking a mild 21-hydroxylase activity deficiency. Levels of ACTH may increase due to the lack of negative feedback by cortisol, further exacerbating androgen production. These patients often present with hirsutism, acne, and anovulation. Thus, late-onset CAH may mimic polycystic ovarian syndrome (PCOS).

Diagnostically, serum 17-hydroxyprogesterone (17-OH-P) levels provide a sensitive screen for the presence of CAH. Levels should be measured during the follicular phase to avoid false-positives from 17-OH-P secretion by the corpus luteum.

Synthesis of Estrogens from Androgens

Aromatization of C19 androgens by P450arom (aromatase; CYP19) yields C18 estrogens containing a phenolic ring (see Fig. 10-1). In addition to the ovary, aromatase is expressed in significant levels in adipose tissue, skin, and brain (Simpson, 1997). Clinically important, sufficient estrogen can be derived from peripheral aromatization to produce endometrial bleeding in postmenopausal women, especially those who are overweight or obese.

5α-Reductase Types 1 and 2

The 5α-reductase enzyme exists in two forms, each encoded by a separate gene. The type 1 enzyme is found in the liver, kidneys, skin, and brain. In contrast, the type 2 enzyme is predominantly expressed in the male genitalia (Russell, 1994; Wilson, 1993). 5α-reductase converts testosterone to a more potent androgen, 5α-dihydrotestosterone (DHT). Because DHT promotes transformation of vellus hair to terminal hair, medications that antagonize 5α-reductase are often effective in the treatment of hirsutism (see Chap. 17, Hirsutism).

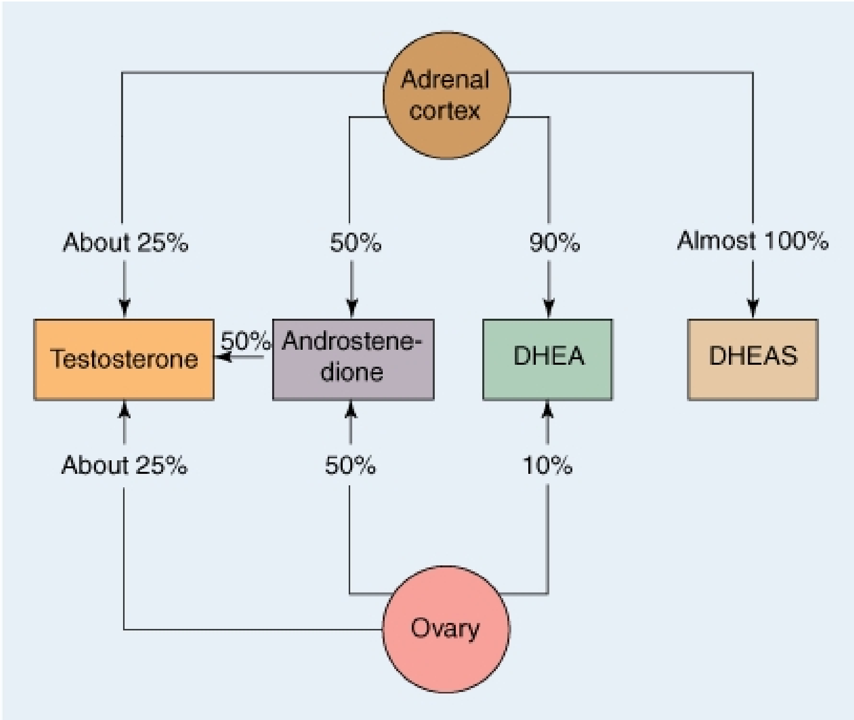
DERIVATION OF CIRCULATING ESTROGENS IN THE FEMALE

Circulating estrogens in the reproductive-aged female are a mixture of both estradiol and the less potent estrone. Although a small amount of estriol is produced through peripheral conversion in the nonpregnant female, estriol production is primarily limited to production by the placenta during pregnancy.

Estradiol is the primary estrogen produced by the ovary during reproductive years. Levels are derived from both direct synthesis in developing follicles and through conversion of estrone. Estrone is secreted directly by the ovary and can be converted from androstenedione in the periphery. Androgens are converted to estrogens in many tissues, but mainly result from aromatase activity in skin and adipose tissue.

The ovary produces primarily androstenedione and dehydroepiandrosterone (DHEA) with small amounts of testosterone. Although the adrenal cortex primarily produces mineralocorticoids and glucocorticoids, it also contributes to approximately one-half of the daily production of androstenedione, DHEA, and essentially all of the sulfated form of DHEA (DHEAS). Twenty-five percent of circulating testosterone is secreted by the ovary, 25 percent is secreted by the adrenal gland, and the remaining 50 percent is produced by peripheral conversion of androstenedione to testosterone (Fig. 15-14) (Silva, 1987).

FIGURE 15-14



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Diagram depicts the contribution of the adrenal glands and ovaries to levels of androgens, dehydroepiandrosterone (DHEA), and DHEA-sulfate (DHEAS). *(Redrawn from Speroff, 1994, with permission.)*

STEROID SYNTHESIS IN THE ADRENAL GLAND

The adult adrenal gland is composed of three zones. Each of these zones expresses a different complement of steroidogenic enzymes and as a result, synthesizes different products. The zona glomerulosa lacks 17α-hydroxylase activity but contains large amounts of aldosterone synthase (P450aldo) and therefore produces mineralocorticoids. As noted earlier, the zona fasciculata and zona reticularis, both of which express the 17α-hydroxylase gene, synthesize glucocorticoids and androgens, respectively (Corticotropin-Releasing Hormone).

STEROID HORMONE TRANSPORT IN THE CIRCULATION

Most steroids in the peripheral circulation are bound to carrier proteins, either specific proteins such as sex-hormone binding globulin (SHBG) or corticosteroid-binding globulin, or to nonspecific proteins such as albumin. Only 1 to 2 percent of androgens and estrogens are unbound or free.

Only the unbound steroid fraction is believed to be biologically active, although albumin's low affinity for sex steroids may allow steroids bound to this protein to exert some effects. The amount of free hormone is in equilibrium with the amount bound. As a result, small changes in carrier protein expression can produce substantial alterations in steroid effect.

Sex-hormone binding globulin (SHBG) circulates as a homodimer that binds a single steroid molecule. This binding protein is primarily synthesized in the liver, although it has also been detected in other tissues such as the brain, placenta, endometrium, and testes (Hammond, 1989, 1996). Levels of SHBG are increased by hyperthyroidism, pregnancy, and estrogen administration. In contrast, androgens, progestins, GH, insulin, and corticoids decrease SHBG levels. An increase in weight, particularly central body fat, can significantly blunt SHBG expression and thereby increase free hormone levels.

Note that unbound hormone can be technically difficult to measure and results should be interpreted with caution. Free testosterone levels are the most commonly ordered free steroid hormone tests. The most accurate assays require dialysis of the sample and are performed by a limited number of commercial laboratories. The more widely available calculated free levels are relatively inaccurate. Unlike thyroid hormone measurements, the measurement of free testosterone is rarely necessary for clinical diagnosis in the female. For example, measurement of testosterone levels in patients with presumed PCOS are important for eliminating the presence of an androgen-producing tumor. Normal or high-normal levels of total testosterone are consistent with the diagnosis of PCOS. Because testosterone decreases SHBG levels, patients with normal total testosterone levels but clinical evidence of hyperandrogenism (hirsutism and/or acne), invariably have either increased free testosterone levels or increased sensitivity of the hair follicle and sebaceous glands.

RECEPTOR STRUCTURE AND FUNCTION

Steroid hormones and peptide factors differ in their specific DNA interaction, yet both ultimately lead to DNA transcription and protein production. In the nucleus, steroid-bound receptors bind to DNA-regulatory elements within target-gene promoter regions. In the case of peptide factors, sequential phosphorylation ultimately activates proteins bound to gene promoter sequences. In either case, following gene activation, the enzyme ribonucleic acid (RNA) polymerase transcribes the information into messenger ribonucleic acid (mRNA), which carries the coded information into the cytoplasmic compartment of cells. There, the information is translated by ribosomes into proteins.

G-Protein Coupled Receptors

INTRACELLULAR SIGNALING SYSTEMS

G-protein coupled receptors are a large family of cell membrane associated receptors that bind peptide factors. These receptors consist of a hydrophilic extracellular domain, an intracellular domain, and a hydrophobic transmembrane domain that spans the cell membrane seven times. When bound to hormone, these receptors undergo a conformational change, activate intracellular signaling pathways, and through a series of phosphorylation events, ultimately modulate transcription of multiple genes within the target cell.

GONADOTROPIN-RELEASING HORMONE RECEPTOR

The GnRH receptor (GnRH-R) is a member of the G-protein coupled receptor superfamily. Expression of GnRH-R has been identified in the ovary, testes, hypothalamus, prostate, breast, and placenta. Gonadotropin-releasing hormone itself may also be expressed in the pituitary, gonads, and placenta. Although data are still preliminary, GnRH and its receptor may form an autocrine/paracrine regulatory network in reproductive tissues, besides the classic neuroendocrine hypothalamic-pituitary system.

GONADOTROPIN RECEPTORS

Both LH and hCG bind to a single G-protein coupled receptor known as the LH/CG receptor. Relative to LH, hCG has a slightly higher affinity for the receptor and has a longer half-life. In contrast, FSH binds to a unique G-protein coupled receptor.

Within the ovary, the LH/CG receptor is expressed on thecal cells, interstitial cells, and luteal cells. In the granulosa cells of preantral follicles, LH/CG receptor mRNA is nearly undetectable. Expression of this receptor is markedly induced during follicular maturation, with high levels observed in differentiated granulosa cells. LH/CG receptors have been identified in the human endometrium, myometrium, fallopian tubes, and brain (Camp, 1991). The function of the LH/CG ligand-receptor system is unknown for these other tissues. In contrast, FSH receptor expression appears to be restricted to the granulosa cells of the ovary and the Sertoli cells of the testis.

Steroid Hormone Receptors

CLASSIFICATION OF STEROID RECEPTOR SUPERFAMILY MEMBERS

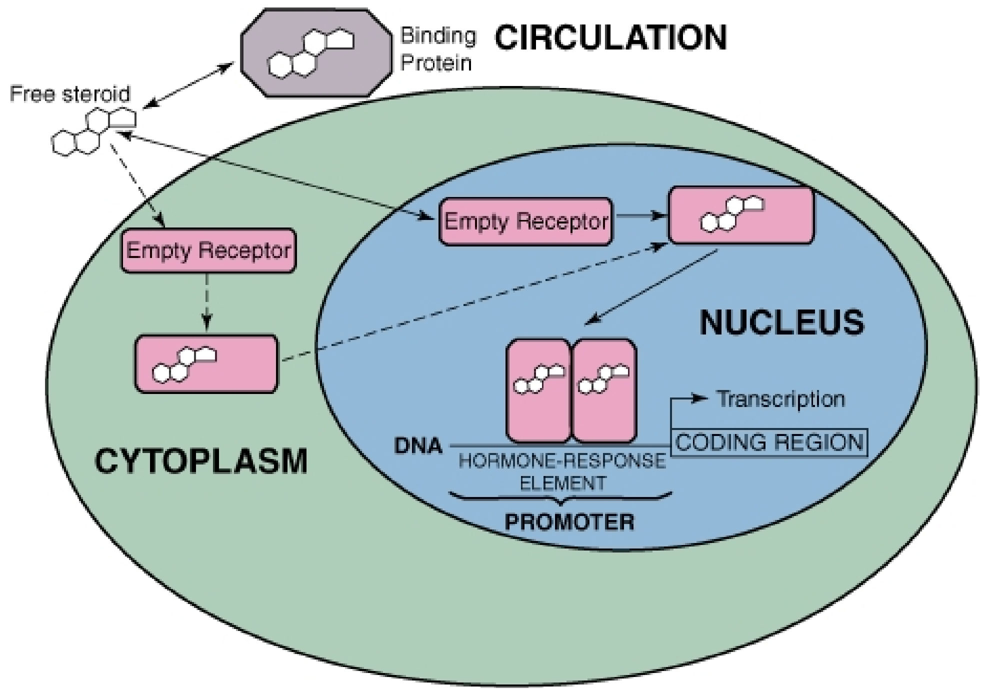
Despite their structural similarities, estrogens, progestins, androgens, mineralocorticoids, and glucocorticoids all interact with unique receptors known as nuclear hormone receptors. The nuclear receptor superfamily consists of three receptor groups: (1) those that bind steroidal ligands, (2) those that have affinity for nonsteroidal ligands, and (3) those with no known ligand. In the

first group, receptors are gene transcription factors with known steroidal ligands, such as estrogen, progesterone, and androgens. The second group contains nonsteroid ligand-activated receptors such as thyroid hormone and retinoic acid receptors. Lastly, orphan receptors comprise the largest component of the nuclear receptor superfamily. By definition, these receptors do not have an identified ligand and may be constitutively active.

MODULAR STRUCTURE OF THE STEROID RECEPTOR SUPERFAMILY

Free steroids diffuse into cells and combine with specific receptors (Fig. 15-15). Subsequently, steroid receptors enhance or repress gene transcription through interactions with specific DNA sequences, called hormone responsive elements, in the promoter region of target genes (Klinge, 2001). Members of this receptor superfamily exhibit a modular structure of distinct domains as depicted in Fig. 15-16. Each of these regions provides activities required for full receptor function.

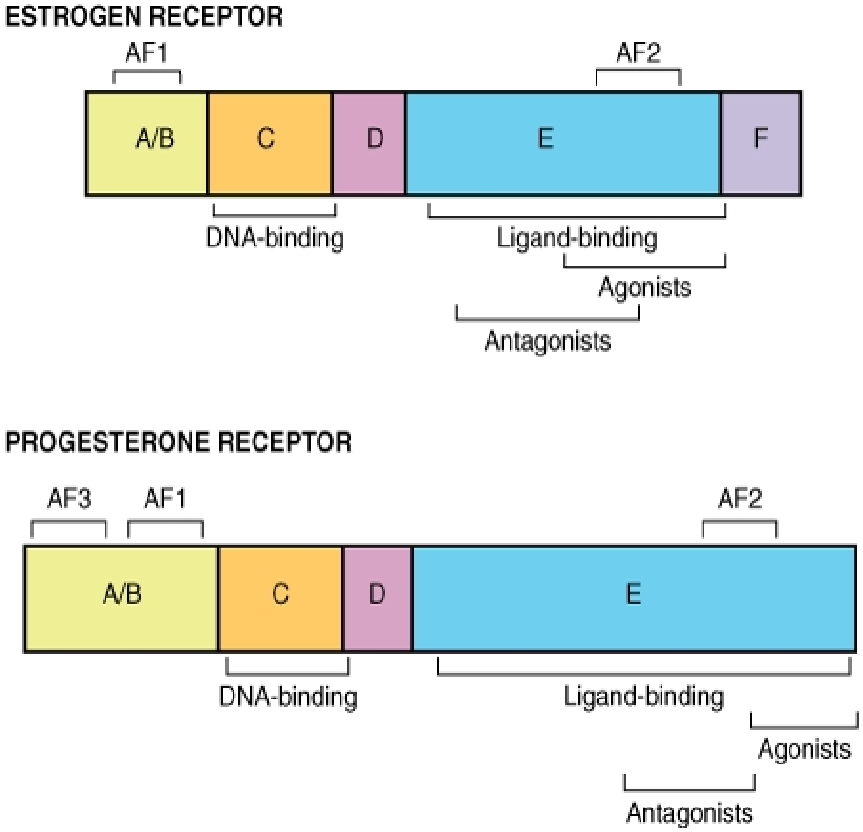
FIGURE 15-15



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Diagram illustrates interaction between cells and steroid hormones. Most hormones circulate bound to carrier serum binding proteins. Unbound hormones are free to bind with empty steroid receptors found either in the cytoplasm or more commonly, in the cell's nucleus. Hormone-bound receptors then bind to specific DNA promoter sequences. This binding typically leads to DNA transcription and eventually to specific protein synthesis. *(From Bulun, 2005, with permission.)*

FIGURE 15-16



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Drawing depicts the concept of functional domains within estrogen and progesterone receptors. Note distinct sites for ligand and DNA binding. *(Redrawn from O'Malley, 1999, with permission.)*

In general, nuclear receptors have two regions that are critical for gene activation, termed activation function 1 and activation function 2 (AF1 and AF2). AF1 is located in the A/B domain and is usually ligand-independent. AF2 is in the ligand-binding domain (E) and is often hormone-dependent. The highly conserved DNA-binding region (C) consists of "zinc fingers", so-called because the presence of zinc introduces a loop in the amino acid sequence, creating a structure that inserts into the DNA helix.

ESTROGEN, PROGESTERONE, AND ANDROGEN RECEPTORS

Receptors for estrogen are localized to the nucleus. In contrast, progesterone receptors (PRs), androgen receptors (ARs), and those for mineralocorticoids and glucocorticoids are cytoplasmic in the absence of ligand. Ligand binding to these latter receptors allows translocation to the nucleus.

Two isoforms of estrogen receptors, ERα and ERβ, have been cloned and are encoded by separate genes. These receptors are differentially expressed in tissues and appear to subserve distinct functions (Kuiper, 1997). For example, both ERα and ERβ are required for normal ovarian function. However, mice lacking ERα are anovulatory and accumulate cystic follicles, whereas the ovaries of ERβ null mice are normal histologically despite impaired ovulation (Couse, 2000).

The progesterone receptor (PR) also exists in at least two isoforms. Encoded from a single gene, PRA and PRB are identical except for an additional 164 amino acids at the amino terminus (Conneely, 2002). A third PR isoform, designated PRC, differs from the other two in its DNA-binding domain and has been postulated to act as a progestin inhibitor (Wei, 1996). As with the estrogen receptors, the PR isoforms are not interchangeable. For example, PRA is required for normal ovarian and uterine functions but is

expendable in the breast (Lydon, 1996).

Only one form of the androgen receptor (AR) has been identified. This receptor contains the classic steroid receptor structure. Mutations in this receptor are responsible for the syndrome of androgen insensitivity in 46,XY patients characterized by lack of sexual hair, absence of a uterus and fallopian tubes, and presence of a vaginal pouch, and intra-abdominal testes (see Chap. 18, Pathophysiology) (Brinkmann, 2001).

Nongenomic Actions of Steroids

Recent studies have introduced the concept that a subset of steroids, including estrogens and progestins, may alter cell function via nongenomic effects, that is, independent of the classic nuclear hormone receptors. These nongenomic effects occur rapidly and may be mediated via cell-surface receptors (Moore, 1999). Pharmacologic agents under development specifically target these nongenomic effects to allow more precise therapy for steroid-sensitive disorders.

Receptor Regulation

Many factors modulate the cellular response to sex steroids and peptide factors. Of these, the number of receptors within a cell or on the cell membrane is critical for attaining a maximal hormonal response. Importantly, the number of receptors cell can be modified at multiple levels of gene expression from gene transcription through receptor protein degradation.

DESENSITIZATION

Hormonally-induced negative regulation of receptors is termed *homologous downregulation* or *desensitization* . Desensitization provides a mechanism for limiting the duration of a hormonal response by decreasing the sensitivity of a cell to a constant level of hormone upon prolonged exposure.

Within the reproductive system, the process of desensitization is best understood for the GnRH receptor and is used clinically to produce a hypoestrogenic state. Pharmacologic agonists of GnRH initially stimulate receptors on pituitary gonadotropes to cause a supraphysiologic release of both luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (see Chap. 9, GnRH Agonists). With their long-term action, however, agonists downregulate receptors in gonadotropes, thus impairing sensitivity to further GnRH stimulation. Correspondingly, decreased gonadotropin secretion leads to suppressed estrogen and progesterone levels 1 to 2 weeks after initial GnRH agonist administration.

HORMONE MEASUREMENT

Potential Measurement Inaccuracy

Immunoassays have been developed for essentially all polypeptide, steroid, and thyroid hormones. These assays are remarkably sensitive, and in most cases are easily automated. For many hormones, the concentration is reported as International Units per volume rather than as a mass per volume (Table 15-4). It is critical to know which reference standard is used by a specific assay, as results may differ significantly. Reference preparations are produced by the World Health Organization (WHO) or by the National Institutes of Health (NIH). Over 20 standards are available for measurement of LH, FSH, PRL, and hCG. Clinically, this issue may arise in a patient with a possible ectopic pregnancy in which serial β-hCG levels are being obtained at different health care facilities.

Table 15-4 Reference Ranges for Selected Reproductive Steroids in Adult Human Serum

Steroid	Subjects	Reference Values
Androstenedione	Men	2.8â€“7.3 nmol/L
	Women	3.1â€“12.2 nmol/L
Testosterone	Men	6.9â€“34.7 nmol/L
	Women	0.7â€“2.8 nmol/L

Dihydrotestosterone	Men	1.0â€“3.10 nmol/L
	Women	0.07â€“.086 nmol/L
Dehydroepiandrosterone	Men/Women	5.5â€“24.3 nmol/L
Dehydroepiandrosterone sulfonate	Men/Women	2.5â€“10.4 µmol/L
Progesterone	Men	<0.3â€“1.3 nmol/L
	Women	
	Follicular	0.3â€“3.0 nmol/L
	Luteal	19.0â€“45.0 nmol/L
Estradiol	Men	<37â€“210 pmol/L
	Women	
	Follicular	<37â€“360 pmol/L
	Luteal	625â€“2830 pmol/L
	Midcycle	699â€“1250 pmol/L
	Postmenopausal	<37â€“140 pmol/L
Estrone	Men	37â€“250 pmol/L
	Women	
	Follicular	110â€“400 pmol/L
	Luteal	310â€“660 pmol/L
	Postmenopausal	22â€“230 pmol/L
Estrone sulfonate	Men	600â€“2500 pmol/L
	Women	
	Follicular	700â€“3600 pmol/L
	Luteal	1100â€“7300 pmol/L
	Postmenopausal	130â€“1200 pmol/L

From O'Malley, 1999, with permission.

The possibility of a "hook effect" should also be considered in the interpretation of results. In the presence of very high hormone levels, antibody binding will be saturated and can give a falsely low reading.

In addition, the amount of immunoreactive hormone present in a sample does not necessarily correlate with the biologic activity of that hormone. For example, PRL exists in multiple isoforms, many of which are immunologically detectable, but not biologically

active. Similarly, alternate glycosylation patterns of the gonadotropins at different times of the reproductive life span are believed to alter their biologic activity.

"Normal" ranges should also be interpreted with care, as a stated normal range is often broad. An individual may have a doubling of their hormone level, and the level may still lie within a normal range, although the result is actually abnormal for that individual.

In the context of the pituitary gland and its target endocrine glands, it may be adequate to measure the pituitary hormone alone. However, interpretation of the result may be clarified by the addition of the target hormone level. For example, in many laboratories, an abnormal TSH value will lead to "reflex" testing for thyroid hormone levels. Low levels of both members of a stimulating-hormone and target-gland hormone pair indicate an abnormality in either hypothalamic or pituitary function (Table 15-5). High levels of a target-gland hormone coupled with low levels of its stimulating pituitary hormone suggest autonomous secretion by the target organ, such as that which occurs in the hyperthyroidism of Graves disease.

Table 15-5 Classification of Functional Amenorrhea

Description	LH/FSH	Estrogen
Hyper gonadotropic	High	Low
Hypo gonadism		
Hypo gonadotropic	Low	Low
Hypo gonadism		

FSH = follicle-stimulating hormone; LH = luteinizing hormone.

Stimulation Tests

These tests may be used when hypofunction of an endocrine organ is suspected. These tests use a known endogenous stimulating hormone to assess the reserve capacity of the tissue of interest. The trophic hormone used may be a hypothalamic releasing factor such as GnRH or TRH, or a substitute pituitary hormone such as hCG for LH or cortrysyn for ACTH. The ability of the target gland to respond is measured by an increase in the appropriate hormone's plasma level. The "GnRH stim" test may be useful in evaluation of delayed puberty (see Chap. 14, Central Precocious Puberty (Gonadotropin-Dependent)). Unfortunately, clinical grade GnRH is often unavailable.

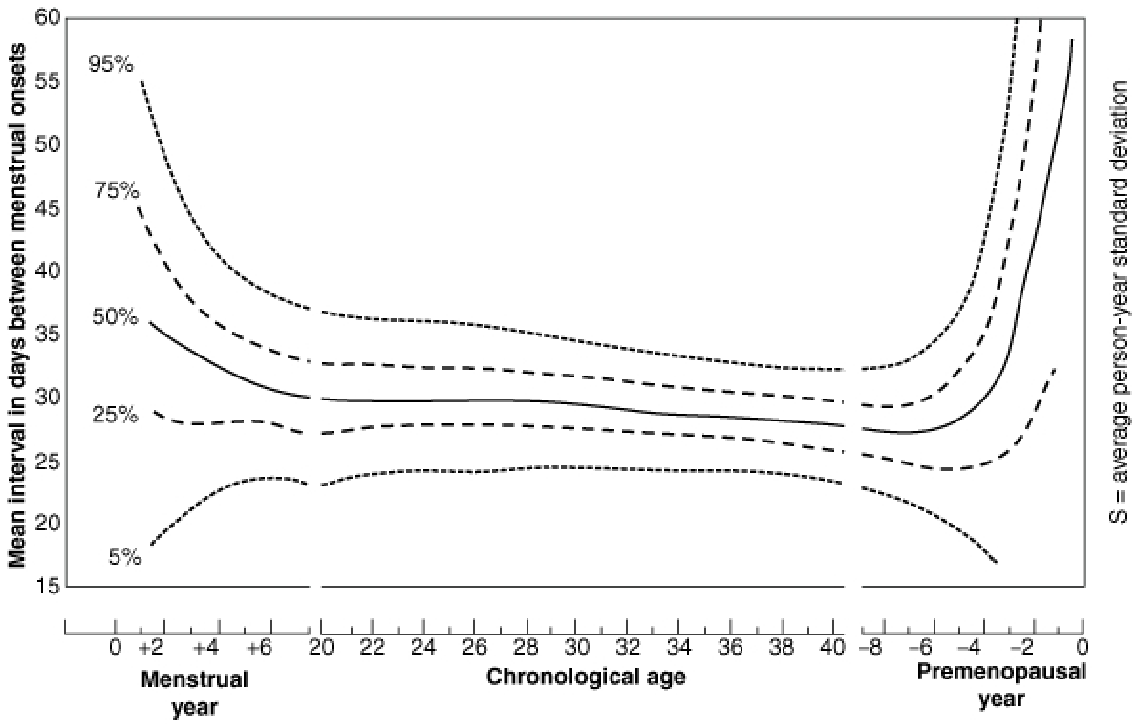
Suppression Tests

These tests may be performed when endocrine hyperfunction is suspected. For example, a dexamethasone suppression test may be given to a patient with suspected hypercortisolism (Cushing disease or syndrome) to gauge the ability of this treatment to inhibit ACTH secretion and thus cortisol production by the adrenal (see Chap. 17, Cortisol). The failure of glucocorticoid treatment to suppress cortisol production would be consistent with primary hyperadrenalism.

MENSTRUAL CYCLE

The typical menstrual cycle is defined as 28 Â± 7 days, with menstrual flow lasting 4 Â± 2 days, and an average blood loss of 20 to 60 mL. By convention, the first day of vaginal bleeding is considered day 1 of the menstrual cycle. Menstrual cycle intervals vary among women and often for an individual woman at different times of her reproductive life (Fig. 15-17). In a study of more than 2,700 women, menstrual cycle interval was most irregular in the 2 years following menarche and the 3 years preceding menopause (Treloar, 1967). The menstrual cycle is least variable between the ages of 20 and 40 years. Specifically, a trend toward shorter intervals is common during early menopausal transition, but is followed by interval lengthening in later transition (see Chap. 21, Definitions).

FIGURE 15-17



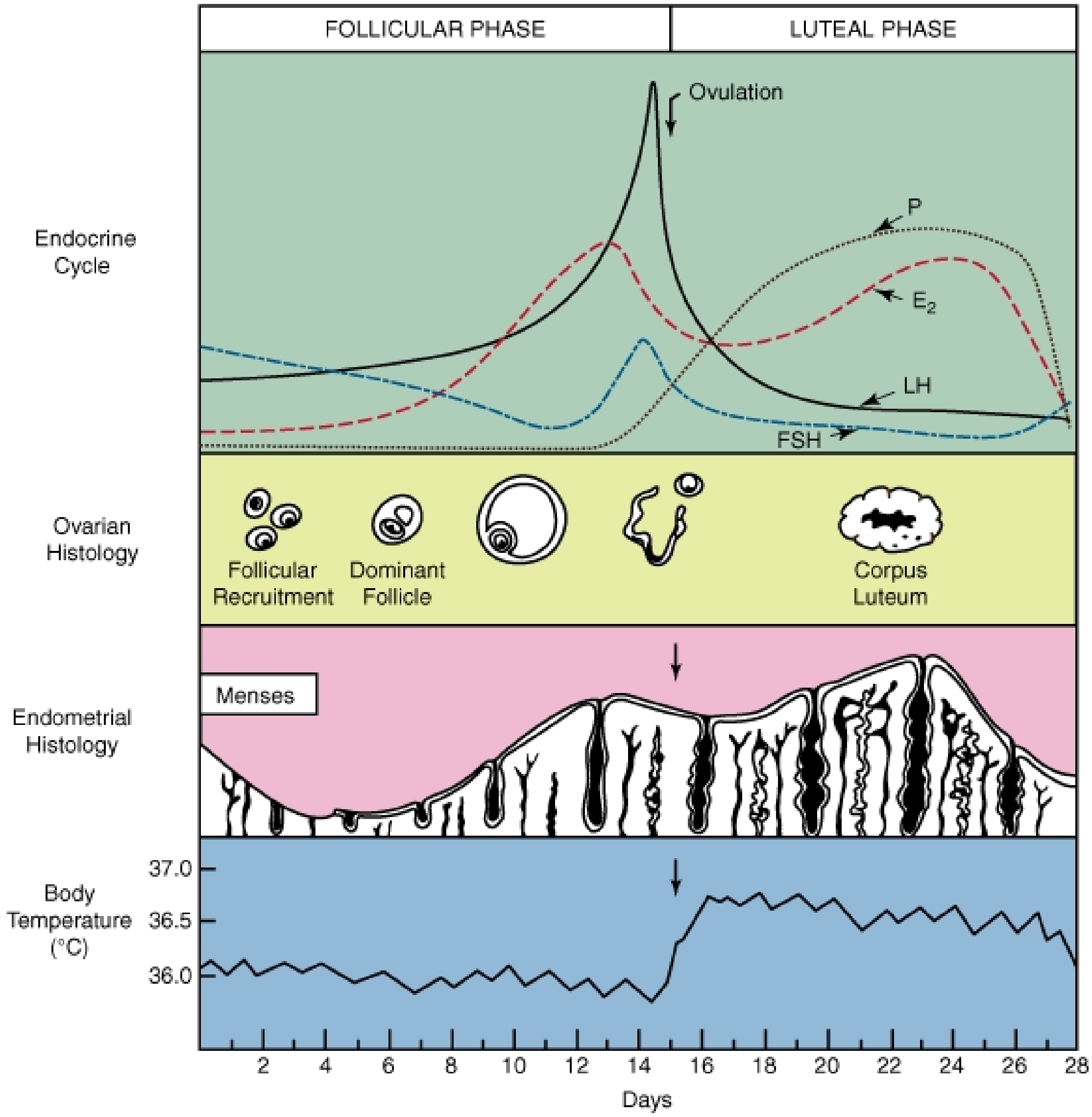
Graphic depiction of menstrual cycle length variation with age. *(Redrawn from Treloar, 1967, with permission.)*

When viewed from a perspective of ovarian function, the menstrual cycle can be divided into a pre-ovulatory follicular phase and postovulatory luteal phase (Fig. 15-18). Corresponding phases in the endometrium are termed the proliferative and secretory phases (Table 15-6). For most women, the luteal phase of the menstrual cycle is stable, lasting 13 to 14 days. Thus, variations in normal cycle length generally result from variations in follicular phase duration (Ferin, 1974).

Table 15-6 Menstrual Cycle Characteristics

Menstrual Phases			
Cycle Day	1â€"5	6â€"14	15â€"28
Ovarian phase	Early follicular	Follicular	Luteal
Endometrial phase	Menstrual	Proliferative	Secretory
Estrogen/Progesterone	Low levels	Estrogen	Progesterone

FIGURE 15-18



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

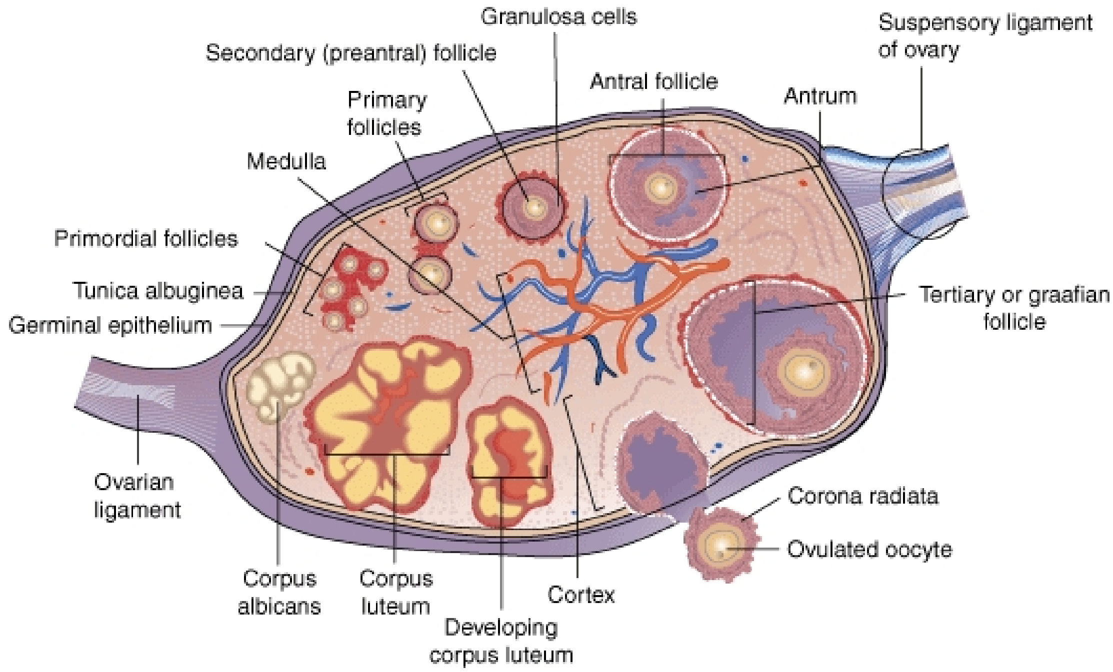
Drawing depicts: (1) gonadotropin and sex steroid level changes, (2) oocyte development, (3) endometrial changes, and (4) basal body temperature changes within a normal menstrual cycle. E_2 = estrogen; FSH = follicle-stimulating hormone; LH = luteinizing hormone; P = progesterone. *(From Carr, 2005a, with permission.)*

THE OVARY

Ovarian Morphology

The adult human ovary is oval with a length of 2 to 5 cm, a width of 1.5 to 3 cm, and a thickness of 0.5 to 1.5 cm. During the reproductive years, ovaries weigh between 5 and 10 g. They are comprised of three parts: an outer cortical region, which contains both the germinal epithelium and the follicles; a medullary region, which consists of connective tissue, myoid-like contractile cells, and interstitial cells; and a hilum, which contains blood vessels, lymphatics and nerves that enter the ovary (Fig. 15-19).

FIGURE 15-19



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Drawing depicts ovarian anatomy and various sequential steps of follicular development. *(From McKinley, 2006, with permission.)*

Ovaries have two interrelated functions: the production of oocytes and the production of steroid and peptide hormones that create an environment in which fertilization and subsequent implantation in the endometrium can occur. Endocrine functions of the ovary correlate closely with the morphologic appearance and disappearance of follicles and corpus luteum.

Embryology of the Ovary

The ovary develops from three major cellular sources: (1) primordial germ cells, which arise from the endoderm of the yolk sac and differentiate into the primary oogonium, (2) coelomic epithelial cells, which develop into granulosa cells, and (3) mesenchymal cells from the gonadal ridge, which become the ovarian stroma.

Primordial germ cells can be identified in the yolk sac as early as the third week of gestation (Baker, 1963). These cells begin their migration into the gonadal ridge during the sixth week of gestation and generate the primary sex cords (see Fig. 18-2). It is not possible to distinguish the ovary from the testes by histologic criteria until approximately 10 to 11 weeks of fetal life.

After the primordial cells reach the gonad, they continue to multiply through successive mitotic divisions. Starting at 12 weeks' gestation, a subset of oogonia will enter meiosis to become primary oocytes (Baker, 1967). Primary oocytes are surrounded by a single layer of flattened granulosa cells, creating a primordial follicle.

The Ovary Across the Reproductive Life Span

All oogonia either develop into primary oocytes or become atretic. Based on our current understanding of ovarian function, additional oocytes cannot be generated postnatally. This differs markedly from the male situation in which sperm are produced continuously throughout adulthood.

The maximal number of oogonia is achieved at the 20th week of gestation, at which time six to seven million oogonia are present in the ovary (Baker, 1963). Approximately one to two million oogonia are present at birth with less than 400,000 present at the initiation of puberty, of which less than 500 are destined to ovulate (Peters, 1978). Therefore, most female germ cells are lost

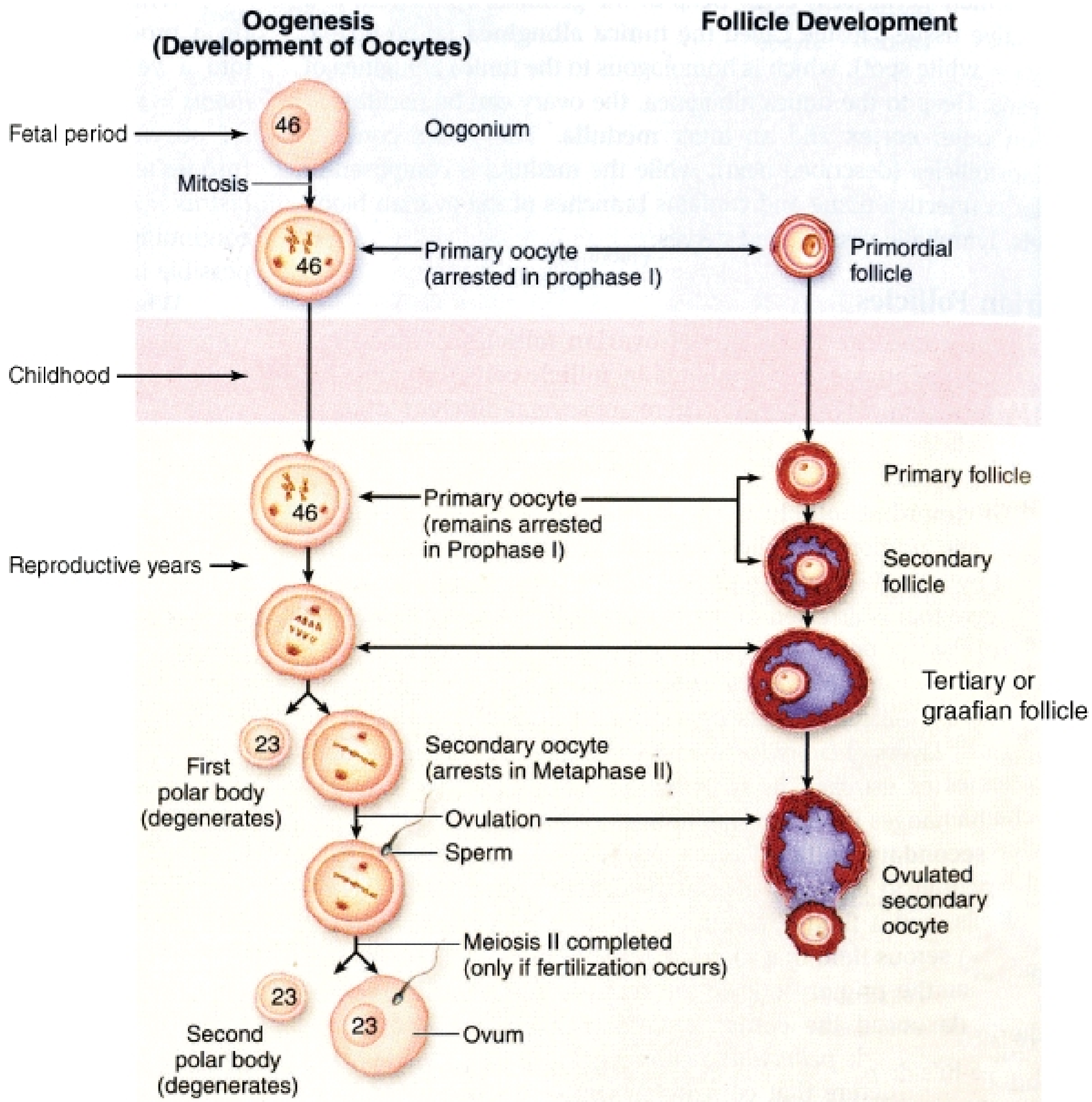
through atresia (see Fig. 14-1) (Hsueh, 1996).

There is now strong evidence that follicular atresia is not a passive, necrotic process, but rather a precisely controlled active process, namely apoptosis, which is under hormonal control. Apoptosis begins in utero and continues throughout reproductive life.

Meiotic Division during Oocyte Maturation

As previously mentioned, primary oogonia enter meiosis in utero to become primary oocytes. These oocytes are arrested in development at prophase I during the first meiotic division. Meiotic division resumes at ovulation in response to the LH surge. Once again, the process is arrested. The arrest of meiosis prior to ovulation is believed to be due to production of an oocyte maturation inhibitor (OMI) by the granulosa cells (Tsafriri, 1982). Meiosis is completed only if fertilization occurs (Fig. 15-20).

FIGURE 15-20



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Drawing illustrates the steps of meiosis and the corresponding stages of oocyte development. In the fetal period, mitotic division of oocytes produces primary oocytes. Primary oocytes begin meiosis, but the process arrests in the first meiotic prophase. In childhood, primary oocytes

remain suspended in prophase I. Beginning in puberty and extending through the reproductive years, several primordial follicles mature each month into primary follicles. A few of these continue development to secondary follicles. One or two secondary follicles progress to a tertiary or graafian follicle stage. At this stage, the first meiotic division occurs to produce a haploid secondary oocyte and a polar body. During this process, cytoplasm is conserved by the secondary oocyte, and consequently the polar body is disproportionately small. The secondary oocyte halts meiosis at its second metaphase. One of the secondary oocytes is released at ovulation. If the oocyte is fertilized, then completion of the second meiotic division follows. If fertilization fails to occur, then the oocyte degenerates prior to completion of the second meiotic division. *(From McKinley, 2006, with permission.)*

Completion of the first meiotic division within the oocyte results in production of a polar body, which contains chromosomal material but minimal cytoplasm. With completion of meiosis following fertilization, a second polar body is extruded. The maternal nucleus, called a pronucleus, fuses with the paternal pronucleus to generate a pre-embryo with a 46,XX or 46,XY karyotype (Felig, 1987).

Stromal Cells

Ovarian stroma contains interstitial cells, connective tissue cells, and contractile cells. Of these, connective tissue cells provide structural support to the ovary. Interstitial cells surrounding a developing follicle differentiate into theca cells. Under gonadotropin stimulation, these cells increase in size and develop lipid stores, which are characteristic of steroid-producing cells (Saxena, 1972).

Another group of interstitial cells is present in the ovarian hilum and therefore are known as hilus cells. These cells closely resemble testicular Leydig cells, and hyperplasia or neoplastic changes in hilar cells may result in virilization from excess testosterone secretion. The normal role of these cells is unknown, but their intimate association with blood vessels and neurons suggest that they may convey systemic signals to the remainder of the ovary (Upadhyay, 1982).

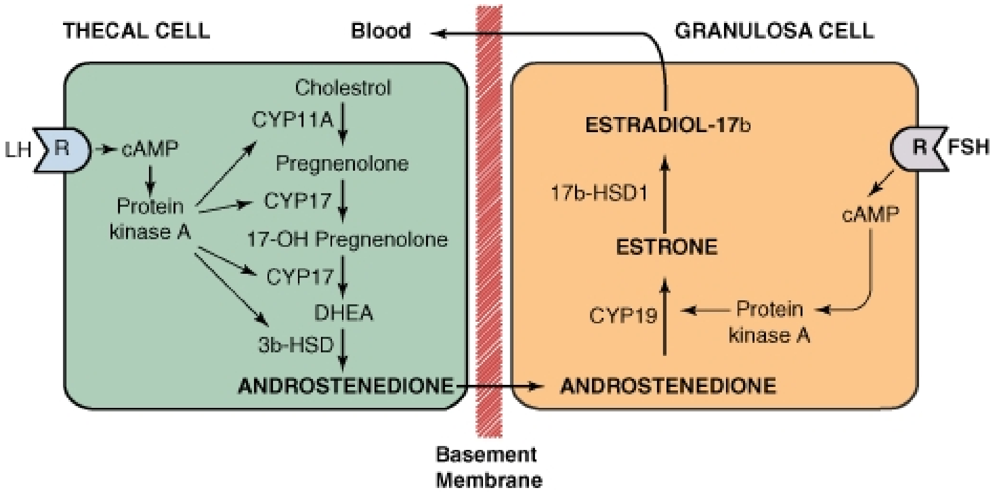
Ovarian Steroidogenesis

The normal functioning ovary synthesizes and secretes the sex-steroid hormonesâ€”estrogens, androgens, and progesterone, in a precisely controlled pattern determined in part by the pituitary gonadotropins, FSH and LH. The most important secretory products of ovarian steroid biosynthesis are progesterone and estradiol. However, the ovary also secretes quantities of estrone, androstenedione, testosterone, and 17-hydroxyprogesterone. Sex-steroid hormones play an important role in the menstrual cycle by preparing the uterus for implantation of a fertilized ovum. If implantation does not occur, ovarian steroidogenesis declines, the endometrium degenerates, and menstruation ensues.

TWO-CELL THEORY OF OVARIAN STEROIDOGENESIS

First proposed by Falck in 1959, the two-cell theory of ovarian steroidogenesis explains that estrogen biosynthesis requires the combined action of two gonadotropins (LH and FSH) on two cell types (theca and granulosa cells) (Fig. 15-21) (Peters, 1980). Until the late antral stage of follicular development, LH-receptor expression is limited to the thecal compartment and FSH-receptor expression is limited to the granulosa cells.

FIGURE 15-21



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Diagram illustrates the two-cell theory of ovarian follicular steroidogenesis. Theca cells contain large numbers of luteinizing hormone (LH) receptors (R). Binding of LH to these receptors leads to cyclic AMP activation and synthesis of androstenedione from cholesterol. Androstenedione diffuses across the basement membrane of theca cells to enter granulosa cells of the ovary. Here, under the activation of follicle-stimulating hormone (FSH), androstenedione is converted by the enzyme aromatase to estrone and estradiol. cAMP = cyclic adenosine monophosphate; CYP11A = cholesterol side-chain cleavage enzyme; CYP17 = 17α-hydroxylase; CYP19 = aromatase; DHEA = dehydroepiandrosterone; 3β-HSD = 3β-hydroxysteroid dehydrogenase; 17β-HSD1 = 17β-hydroxysteroid dehydrogenase; R = receptor. *(From Carr, 2005a, with permission.)*

Theca cells express all of the genes needed to produce androstenedione. This includes high levels of *CYP17* gene expression, whose enzyme product catalyzes 17-hydroxylationâ€"the rate-limiting step in the conversion of progesterones to androgens (Sasano, 1989). This enzyme is absent in the granulosa cells, so they are incapable of producing the precursor needed to produce estrogens by themselves. Granulosa cells therefore rely on the theca cells as their primary source for estrogen precursors.

In response to LH stimulation, theca cells synthesize the androgens, androstenedione and testosterone. These androgens are secreted into the extracellular fluid and diffuse across the basement membrane to the granulosa cells to provide precursors for estrogen production. In contrast to theca cells, granulosa cells express high levels of aromatase activity in response to FSH stimulation. Thus, these cells efficiently convert androgens to estrogens, primarily the potent estrogen, estradiol. In sum, ovarian steroidogenesis is dependent on the effects of LH and FSH acting independently on the theca cells and granulosa cells, respectively.

STEROIDOGENESIS ACROSS THE LIFE SPAN

Childhood

The human ovary has the capacity to produce estrogens by 8 weeks' gestation, however, a minimal amount of steroid is actually synthesized at any time during fetal development (Miller, 1988).

Circulating levels of the gonadotropins, LH and FSH, vary markedly at different ages of a woman's life. During the second trimester of fetal development, the plasma levels of gonadotropins rise to levels similar to those observed in menopause (Faiman, 1976). The fetal hypothalamic-pituitary axis continues to mature during the second trimester of pregnancy, becoming more sensitive to the high circulating levels of estrogen and progesterone secreted by the placenta (Kaplan, 1976; Yen, 1986). In response to the high levels of these steroids, fetal gonadotropins fall to low levels prior to birth. After delivery, gonadotropin levels rise abruptly in the neonate due to separation from the placenta and subsequent freedom from inhibition by placental steroids (Winter, 1976).

The elevated levels of gonadotropins in the newborn persist for the first few months of life, declining to low levels in early childhood

(Winter, 1976). There may be multiple etiologies for the low gonadotropin levels during this period of life. The hypothalamic-pituitary axis has been found to have increased sensitivity to negative feedback, even by the low circulating levels of gonadal steroids at this stage (Yen, 1986). There is growing evidence that there is an intrinsic role of the central nervous system in maintaining low gonadotropin levels. In support of this mechanism, low levels of LH and FSH are found in children with gonadal dysgenesis (Conte, 1975).

Puberty

One of the first signs of puberty is a sleep-associated increase in LH secretion (Fig. 15-22). Over time, increased gonadotropin secretion is noted throughout the day. An increased FSH:LH ratio is typical in the premenarchal girl and postmenopausal woman. During the reproductive years, LH exceeds FSH levels, reversing this ratio.

FIGURE 15-22

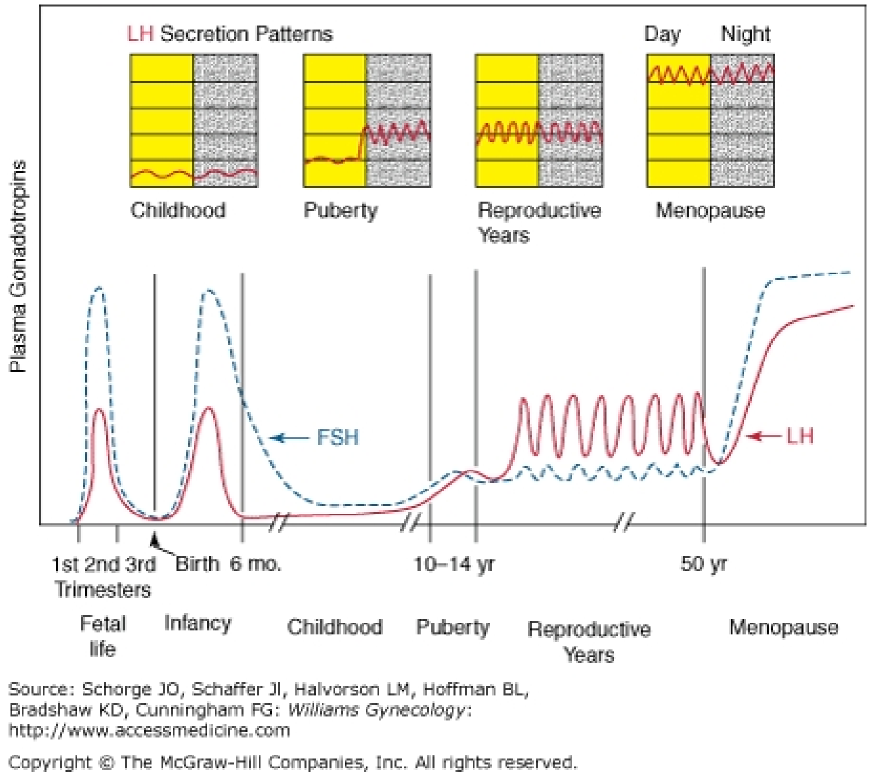


Diagram illustrates variations in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) during different life stages in the female. *(From Carr, 1998, with permission.)*

Increased gonadotropin levels stimulate ovarian estradiol production. The rise in estrogen levels results in the growth spurt, maturation of the female internal and external genitalia, and development of a female habitus including breast enlargement (thelarche). Activation of the pituitary-adrenal axis results in an increase in adrenal androgen production and the associated development of axillary and pubic hair (adrenache or pubarche). Increased gonadotropin levels ultimately lead to ovulation and subsequent menses, with the timing of the first menstrual period defining menarche. This developmental process takes approximately 3 to 4 years.

Postmenopause

The postmenopausal ovary contains only a few follicles, and as a result, plasma estrogen and inhibin levels decrease markedly after cessation of ovulatory cycles. Through loss of this negative feedback, LH and FSH levels are strikingly elevated in postmenopausal women. Elevated LH levels can stimulate production of C_{19} steroids (mainly androstenedione) in ovarian stromal cells. This ovarian-derived androstenedione as well as adrenal androgens can be converted by peripheral tissues to estrone, the principal

estrogen in the plasma of postmenopausal women. The major site for the conversion of androstenedione to estrone is adipose tissue. Peripheral conversion of circulating androstenedione to estrone is higher in postmenopausal women than in premenopausal women of a given body weight, and is directly correlated with body weight. These low circulating estrogen levels are usually inadequate to protect against bone loss.

Follicular Development

Follicular development begins with primordial follicles that were generated during fetal life (see Fig. 15-20). Each follicle consists of an oocyte arrested in the first meiotic division surrounded by a single layer of flattened granulosa cells. These follicles are separated from the stroma by a thin basement membrane. Pre-ovulatory follicles are avascular. As a result, they are critically dependent on diffusion, and later gap junctions, for obtaining nutrients and clearing metabolic waste. Diffusion also allows passage of steroid precursors from the thecal to the granulosa cell layer.

PRIMARY FOLLICLE

In the next stage of development, the granulosa cells become cuboidal and increase in number to form a pseudostratified layer. The follicle is now termed a *primary follicle* . Intercellular gap junctions develop between adjacent granulosa cells and between granulosa cells and the developing oocyte (Albertini, 1974). These gap junctions allow for the passage of nutrients, ions, and regulatory factors between cells. Gap junctions also allow cells without gonadotropin receptors to receive signals from cells with receptor expression (Fletcher, 1985). As a result, hormone-mediated effects can be transmitted throughout the follicle.

During this stage, the oocyte begins secretion of an acellular coat known as the zona pellucida. The human zona pellucida contains at least three proteins, named ZP1, ZP2, and ZP3. In current physiologic models, receptors on the acrosome head of the sperm recognize ZP3. This interaction results in release of acrosomal contents, penetration of the zona pellucida, and fertilization of the egg. Although the precise mechanism may differ between species, enzymes released from the acrosome induce alterations in ZP2, resulting in hardening of the coat. This process prevents fertilization of the oocyte by more than one sperm (Nixon, 2007).

SECONDARY FOLLICLE

Development of a secondary, or preantral, follicle includes final growth of the oocyte and a further increase in granulosa cell number. The stroma differentiates into the *theca interna* , which is adjacent to the basal lamina, and the *theca externa* , which abuts the surrounding stroma (Eppig, 1979).

TERTIARY FOLLICLE

With ongoing development, follicular fluid begins to collect between the granulosa cells, ultimately producing a fluid filled space known as the antrum. The follicle is now termed a *tertiary follicle* or *antral follicle* . Further accumulation of antral fluid results in a rapid increase in follicular size and development of a preovulatory follicle, also termed a *graafian follicle* .

Granulosa cells in the antral follicle are histologically and functionally divided into two groups. The granulosa cells surrounding the oocyte form the cumulus oophorus, whereas the granulosa cells surrounding the antrum are known as mural granulosa cells.

Antral fluid consists of a plasma filtrate and factors secreted by the granulosa cells. These locally produced factors, which include estrogen and growth factors, are present in substantially higher concentrations in follicular fluid than in the circulation and are likely critical for successful follicular maturation.

GONADOTROPINS AND FOLLICULAR DEVELOPMENT

Early stages of development (up to the secondary follicle) do not require gonadotropin stimulation and thus are said to be gonadotropin-independent. Final follicular maturation requires the presence of adequate amounts of circulating LH and FSH and is therefore said to be gonadotropin-dependent (Butt, 1970). Of note, data are beginning to accumulate that suggest that progression from gonadotropin-independent to gonadotropin-dependent stages is not as abrupt as was previously believed.

CONCEPT OF A SELECTION WINDOW

Follicular development is a multi-step process, which proceeds over at least 3 months, culminating in ovulation from a single follicle. Each month a group of follicles, known as a cohort, begins a phase of semi-synchronous growth. The size of this cohort

appears to be proportional to the number of inactive primordial follicles within the ovaries and has been estimated at three to eleven follicles per ovary in young women (Gougeon, 1994; Hodgen, 1982; Pache, 1990).

It is important to emphasize that the ovulatory follicle is recruited from a cohort that began development two to three cycles prior to the ovulatory cycle. During this time, most follicles will die, as they will not be at an appropriate stage of development during the selection window.

During the luteal-follicular transition, a small increase in FSH levels is responsible for selection of the single dominant follicle that will ultimately ovulate (Schipper, 1998). As previously described, theca cells produce androgens and granulosa cells generate estrogens. Estrogens increase with increased follicular size, enhance the effects of FSH on granulosa cells, and create a feed-forward action on follicles that produce estrogens.

It has also been suggested that the intrafollicular levels of members of the insulin-like growth factor family (IGFs) may synergize with FSH to help select the dominant follicle. Of note, the ovary expresses the potent angiogenic factor, vascular endothelial growth factor (VEGF). Studies have demonstrated elevated levels of VEGF around the follicle that will be selected. This follicle would presumably be exposed to higher levels of circulating factors such as FSH. Conversely, follicles that will undergo atresia have a limited blood supply, presumably due to decreased VEGF expression, which effectively decreases delivery of circulating factors to the follicles (Ravindranath, 1992.)

Granulosa cells also produce inhibin B, which passes from the follicle into the plasma and specifically inhibits the release of FSH, but not of LH, by the anterior pituitary. The combined production of estradiol and inhibin B by the dominant follicle results in the decline of follicular phase FSH levels, and at least in part, may be responsible for the failure of other follicles to reach preovulatory status during any one cycle.

ESTROGEN-DOMINANT FOLLICULAR MICROENVIRONMENT

Ongoing follicular maturation requires the successful conversion from an androgen-dominant microenvironment to an estrogen-dominant microenvironment. At low concentrations, androgens stimulate aromatization and contribute to estrogen production. However, intrafollicular androgen levels will rise if aromatization in the granulosa cells lags behind androgen production by the thecal layer. At higher concentrations, androgens are converted to the more potent 5α-androgens, such as dihydrotestosterone. These androgens inhibit aromatase activity, cannot be aromatized to estrogens, and inhibit FSH induction of LH-receptor expression on the granulosa cells (Hillier, 1980; Jia, 1985; McNatty, 1979b).

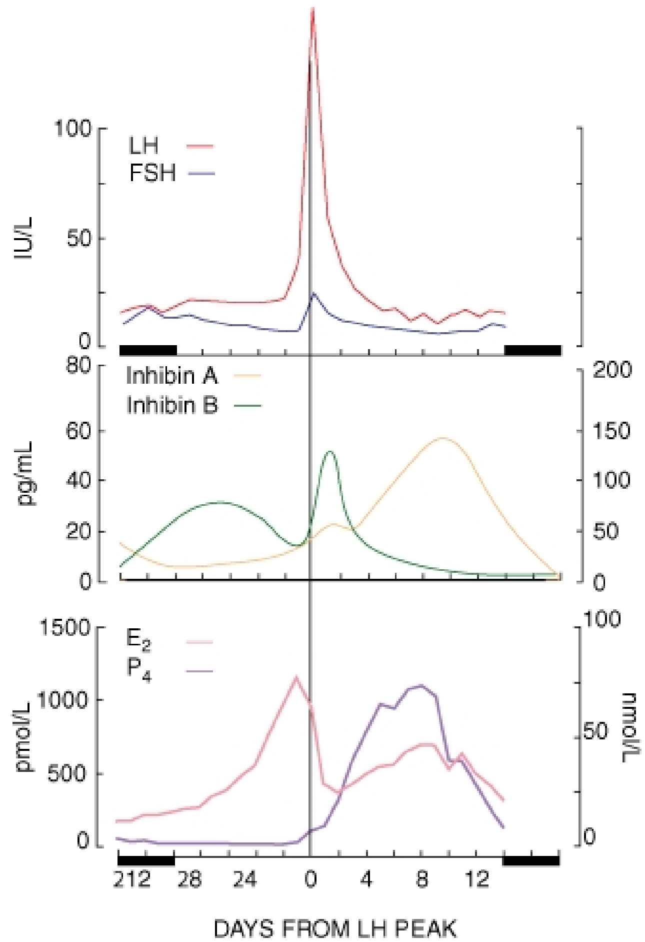
This model predicts that follicles that lack adequate FSH receptor and granulosa cell number will remain primarily androgenic and will therefore become atretic. In support of this model, an increased androgen:estrogen ratio is found in the follicular fluid of atretic follicles and a number of studies have demonstrated that high estrogen levels prevent apoptosis.

Insulin-like growth factor also has apoptosis-suppressing activity, and is produced by granulosa cells. This action of IGF-I is suppressed by certain IGF-binding proteins that are present in the follicular fluid of atretic follicles. The action of FSH to prevent atresia may therefore result, in part, from its ability to stimulate IGF-I synthesis and suppress the synthesis of the IGF-binding proteins.

Follicular Phase

During the end of a previous cycle, estrogen, progesterone, and inhibin levels decrease abruptly. This is followed by a corresponding increase in circulating FSH levels (Fig. 15-23) (Hodgen, 1982). As just described, this increase in FSH level is responsible for recruitment of the follicle cohort that contains the follicle destined for ovulation. Despite general belief, sonographic studies in women have demonstrated that ovulation does not alternate sides, but occurs randomly from either ovary (Baird, 1987).

FIGURE 15-23



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Graphs display gonadotropin, inhibin, and sex-steroid level changes during a normal menstrual cycle. In the first graph, peaking of luteinizing hormone (LH) (red line) and follicle-stimulating hormone (FSH) (blue line) levels are displayed. In the middle graph, changing levels of inhibin A and inhibin B levels are shown. Note that inhibin B levels (solid green line) peak temporally near the midcycle surge in the LH level, whereas maximal elevation of inhibin A (orange line) occurs several days following this peak. In the third graph, elevations in estradiol levels (pink line) are noted prior to the surge in LH levels and in the midluteal phase. Progesterone levels (purple line) peak in the midluteal phase. E_2 = estradiol; P_4 = progesterone.

In women with waning ovarian function, the FSH level at this time of the cycle is elevated relative to that of younger women, presumably due to a loss of ovarian inhibin production. As a result, measurement of an early follicular or cycle day-3 estradiol level is frequently obtained in infertility clinics. The accelerated increase in serum FSH levels results in more robust recruitment of follicles and may explain both the shortened follicular phase observed in these women and the increased incidence of spontaneous twins.

During the midfollicular phase, follicles produce increased amounts of estrogen and inhibin, resulting in a decline in FSH levels through negative feedback. This drop in FSH levels is believed to contribute to selection of the follicle destined to ovulate, termed the *dominant follicle* . Based on this theory, remaining follicles express decreased numbers of FSH receptors and therefore are unable to respond adequately to declining FSH levels. Also of note, the ovary expresses the potent angiogenic factor, VEGF.

During most of follicular development, granulosa cell responses to FSH stimulation include an increase in granulosa cell number, an

increase in aromatase expression, and in the presence of estradiol, expression of LH receptors on the granulosa cells. With the development of LH-receptor expression during the late follicular phase, granulosa cells begin to produce small amounts of progesterone. This progesterone decreases granulosa cell proliferation, thereby slowing follicular growth (Chaffkin, 1992). Progesterone is primarily responsible for generating the FSH surge (Erickson, 1979; McNatty, 1979a). Progesterone also augments the positive feedback of estrogen as discussed in the following section (Couzinet, 1992). This latter effect may explain the occasional induction of ovulation in anovulatory, amenorrheic women when given progesterone to induce menses.

Ovulation and the Luteinizing Hormone Surge

Ovulation, the process by which the oocyte-cumulus is released from the follicle, has been compared with an inflammatory response. As such, products induced by these signaling cascades include gene products that rupture the follicle and remodel the follicular remnant into a corpus luteum.

Toward the end of the follicular phase, estradiol levels increase dramatically. For reasons that are not completely understood, with this rapid increase, estradiol is no longer inhibitory and instead develops positive feedback effects at both the hypothalamus and anterior pituitary gland to generate the LH surge. Estradiol concentrations of 200 pg/mL for 50 hours are necessary to initiate a gonadotropin surge (Young, 1976).

The LH surge acts rapidly on both the granulosa and theca cells of the preovulatory follicle to terminate the genes involved in follicular expression, while at the same time turning on the expression of genes required for ovulation and luteinization. In addition, the LH surge initiates the re-entry of the oocyte into meiosis, expansion of the cumulus oophorus, synthesis of prostaglandins, and luteinization of granulosa cells. The mean duration of the LH surge is 48 hours with ovulation occurring approximately 36 to 40 hours after the onset of the LH surge (Hoff, 1983; Lemarchand-Beraud, 1982). Abrupt termination of the surge is postulated to be due to acutely increasing steroid and inhibin secretion by the corpus luteum.

The granulosa cells surrounding the oocyte differ from mural granulosa cells in that they do not express LH receptors or synthesize progesterone. Cumulus oophorus granulosa cells develop tight gap junctions between each other and with the oocyte. The cumulus mass that accompanies the ovulating oocyte is believed to be important for providing a rough surface and increased size to improve oocyte "pick up" by the tubal fimbria. This surrounding cell mass may also be important for oocyte health.

Discordant oocyte maturation and luteinization is prevented by the action of locally produced factors, including oocyte maturation inhibitor (OMI) and luteinization inhibitor. Endothelin-1 has been proposed to be the luteinization inhibitor, whereas the identity of the OMI is under active investigation (Tedeschi, 1992). Intrafollicular activin may also help to prevent premature luteinization, as it suppresses progesterone production by granulosa cells (Li, 1992).

Recently, members of an epidermal growth factorâ€"like family, that is, amphiregulin, epiregulin, and beta-cellulin, were found to substitute for both the morphologic and biochemical events triggered by LH, including both expansion of the cumulus and maturation of the oocyte. Thus, these growth factors are part of the downstream cascade that begins with LH binding to its receptor and ends with ovulation.

Based on sonographic surveillance, extrusion of the oocyte only lasts a few minutes (Knobil, 1994). The exact mechanism of this expulsion is poorly defined, but is not due to an increase in follicular pressure (Espey, 1974). The presence of proteolytic enzymes in the follicle, including plasmin and collagenase, suggest that these enzymes are responsible for follicular wall thinning (Beers, 1975). The pre-ovulatory gonadotropin surge stimulates expression of tissue plasminogen activator by the granulosa and theca cells. The surge also decreases expression of plasminogen inhibitor, resulting in a marked increase in plasminogen activity (Piquette, 1993).

Prostaglandins also reach a peak concentration in follicular fluid during the pre-ovulatory gonadotropin surge (Lumsden, 1986). Prostaglandins may stimulate smooth muscle contraction in the ovary, thereby contributing to ovulation (Yoshimura, 1987). Women undergoing infertility treatment are advised to avoid prostaglandin synthetase inhibitors in the pre-ovulatory period to avoid luteinized unruptured follicle syndrome (LUFS) (Priddy, 1990; Smith, 1996). The incidence of LUFS has been estimated at 4.5 percent in cycling women. Significant controversy, however, exists about whether LUFS should be considered pathologic or simply a sporadic event (Kerin, 1983).

Luteal Phase

Following ovulation, the remaining follicular cells left by the ovulated follicle differentiate into the corpus luteum, literally meaning *yellow body* (Corner, 1956). This process, which requires LH stimulation, includes both morphologic and functional changes known as luteinization. The granulosa and theca cells proliferate and undergo hypertrophy to form granulosa-lutein cells and smaller theca-lutein cells, respectively (Patton, 1991). The conversion of a granulosa cell into a large luteal cell is a dramatic example of cellular differentiation.

During corpus luteum formation, the basement membrane that separates granulosa cells from theca cells degenerates and allows vascularization of previously avascular granulosa cells. Capillary invasion begins 2 days after ovulation, reaching the center of the corpus luteum by the fourth day. This increase in perfusion provides these luteal cells with access to circulating low-density lipoprotein (LDL), which is used to provide precursor cholesterol for steroid biosynthesis. This marked increase in blood supply can have clinical implications, as pain from a hemorrhagic corpus luteum cyst is a relatively frequent presentation to emergency rooms.

As might be predicted by its name, steroidogenesis in the corpus luteum is under the primary control of luteinizing hormone from the anterior pituitary gland. Based on its steroidogenic products, the luteal phase is considered progesterone dominant, in contrast to the estrogen dominance of the follicular phase. Increased vascularization, cellular hypertrophy, and an increased number of intracellular organelles transform the corpus luteum into the most active steroidogenic tissue in the body. Maximal levels of progesterone production are observed in the midluteal phase and have been estimated at an impressive 40 mg of progesterone per day. Ovulation can be safely assumed to have occurred if the progesterone level exceeds 3 ng/mL on cycle day 21. A progesterone level greater than 10 to 15 ng/mL generally indicates adequate luteal function and no need for progesterone supplementation in infertile women.

Although progesterone is the most abundant ovarian steroid during the luteal phase, estradiol is also produced in significant quantities. Estradiol levels drop transiently immediately after the LH surge and are followed by a steady increase to reach a maximum during the midluteal phase. The reason for this decrease is not known, but may result from direct inhibition of granulosa cell growth by increasing progesterone levels (Hoff, 1983).

The corpus luteum also produces large quantities of the polypeptide inhibin A. This coincides with a decrease in circulating FSH levels in the luteal phase. If inhibin A levels decline at the end of the luteal phase, FSH levels rise once more to begin selection of a oocyte cohort for the next menstrual cycle.

Gonadotropins and Luteal Function

Normal hormonal function of the corpus luteum depends on adequate serum LH levels, the presence of LH receptors on the luteal cells, and a sufficient number of luteal cells (Vande Wiele, 1970). As a result, it is critical that LH receptor expression on the granulosa cells was appropriately induced during the prior follicular phase. In support of the importance of this hormone for survival of the corpus luteum, it has been demonstrated that blunted serum LH concentrations are correlated with a reduced luteal phase length.

Luteal function is further influenced by gonadotropin levels during the preceding follicular phase. A reduction in LH or FSH secretion is correlated with poor luteal function (McNeely, 1988; Stouffer, 1980). Presumably, a lack of FSH leads to a decrease in the total number of granulosa cells. Furthermore, luteal cells in these suboptimal cycles will have a decreased number of FSH-induced LH receptors and thus will be less responsive to LH stimulation.

Luteolysis

If pregnancy does not occur, the corpus luteum regresses through a process called *luteolysis* . The mechanism for luteolysis is poorly understood, but luteal regression is presumed to be tightly regulated and luteal cycle length varies minimally. Following luteolysis, the blood supply to the corpus luteum diminishes, and progesterone and estrogen secretion drop precipitously. Luteal cells undergo apoptosis and become fibrotic, creating the *corpus albicans* (white body).

If pregnancy occurs, human chorionic gonadotropin (hCG) produced by the early gestation "rescues" the corpus luteum from atresia by binding to and activating the LH receptor on luteal cells. Corpus luteum steroidogenesis, stimulated by hCG, maintains

endometrial stability until placental steroid production is adequate to assume this function late in the first trimester. For this reason, surgical removal of the corpus luteum during pregnancy should be followed by progesterone replacement until approximately 10 weeks' gestation.

Gonadal Peptides

ACTIVIN-INHIBIN-FOLLISTATIN SYSTEM

Ovaries synthesize and secrete a group of peptide factorsâ€”inhibin, activin, and follistatin. Circulating inhibin is believed to be primarily gonadal in origin, as serum levels drop abruptly after castration (Demura, 1993).

Serum inhibin levels vary widely across the menstrual cycle (Groome, 1996; McLachlan, 1987). An inverse relationship between circulating inhibin levels and FSH secretion is seen and is consistent with a negative feedback role for inhibin in regulating FSH secretion. During the early follicular phase, FSH stimulates the secretion of inhibin B by the granulosa cells (Buckler, 1989) (see Fig. 15-23). However, increasing levels of circulating inhibin B blunt FSH secretion later in the follicular phase. During the luteal phase, regulation of inhibin production comes under the control of LH and switches from inhibin B to inhibin A (McLachlan, 1989). Inhibin levels peak during the midluteal phase, decrease with the loss of luteal function, and remain low during the luteal-follicular transition and early follicular phase.

Serum levels of activin, although detectable, are low and remain stable across the menstrual cycle (Demura, 1993). Follistatin levels likewise are unchanged across the reproductive cycle. Furthermore, circulating follistatin levels are similar in GnRH-deficient and postmenopausal women as well as women following oophorectomy (Kettel, 1996; Khoury, 1995). These data strongly suggest that circulating follistatin is not derived from the ovary, although its source remains unknown. Essentially all follistatin is bound to activin throughout the menstrual cycle (McConnell, 1998). Therefore, although the ovary does produce both activin and follistatin, these factors appear to act locally rather than modulate gonadotrope function.

INSULIN-LIKE GROWTH FACTOR (IGF)

The relative roles of IGF-I and IGF-II in mediating ovarian function may differ across species, but current data suggest that IGF-II is more important in the human (el Roeiy, 1993). Gonadotropins stimulate IGF-II production in theca cells, granulosa cells, and luteinized granulosa cells. Insulin-like growth factor receptors are expressed on the theca and granulosa cells, supporting an autocrine/paracrine action in the follicle (Hernandez, 1992). Follicle-stimulating hormone also mediates expression of IGF-binding proteins (IGF-BPs). This system, although complex, allows additional fine-tuning of intrafollicular activity (Adashi, 1991; Thierry van Dessel, 1996).

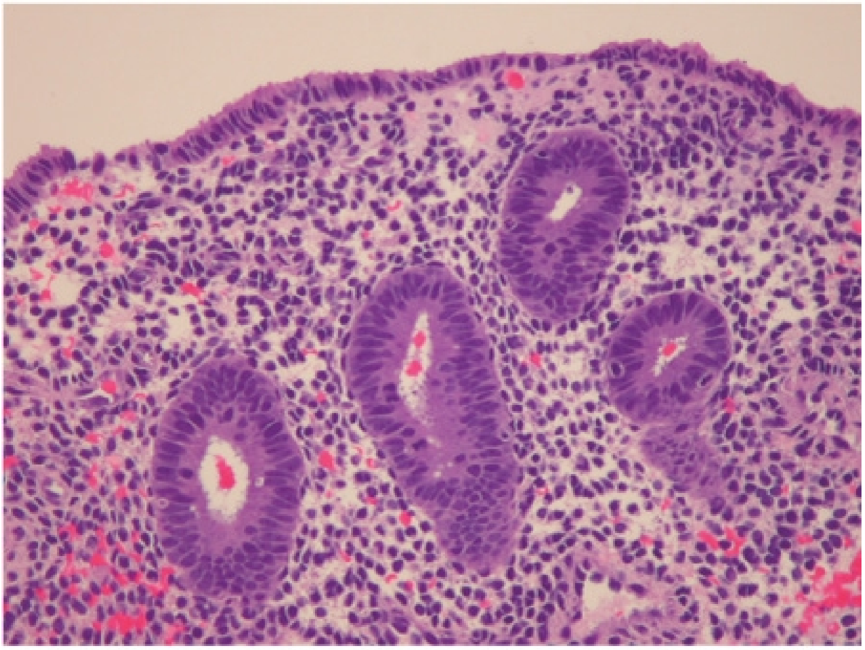
ENDOMETRIUM

Histologic Menstrual Cycle Changes

The endometrium consists of two layers: the *basalis layer,* which lies against the myometrium, and the *functionalis layer,* which is apposed to the uterine lumen. The basalis layer, which does not change significantly across the menstrual cycle, is critical for regeneration of the endometrium following menstrual sloughing. The functionalis layer of the endometrium can be further divided into the superficial, thin, *stratum compactum,* which consists of gland necks and dense stroma, and the underlying *stratum spongiosum,* which contains glands and large amounts of loosely organized stroma and interstitial tissue.

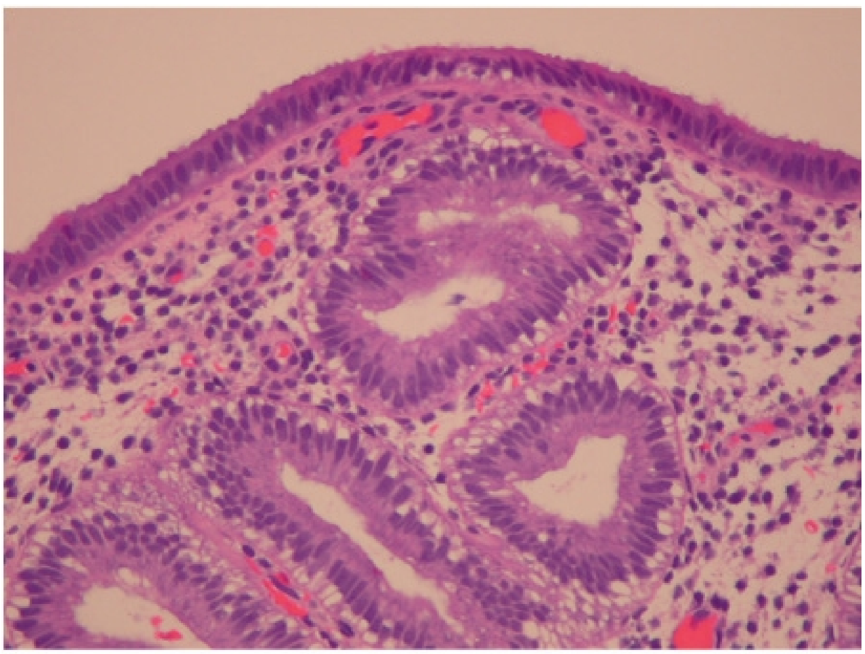
After menstruation, the endometrium is only one to two millimeters thick. Under the influence of estrogen, the glandular and stromal cells of the functionalis layer proliferate rapidly following menses (Fig. 15-24). This period of rapid growth, termed the *proliferative phase,* corresponds to the ovary's follicular phase. As this phase progresses, glands become more tortuous and cells lining the glandular lumen undergo pseudostratification. The stroma remains compact. Endometrial thickness is about 12 millimeters at the time of the LH surge and does not increase significantly thereafter.

FIGURE 15-24



A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



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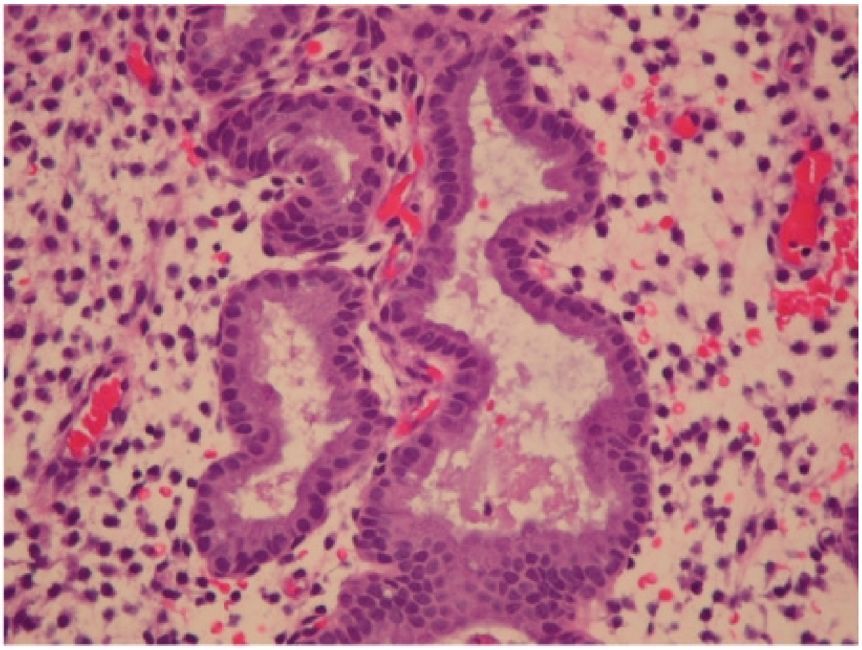
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



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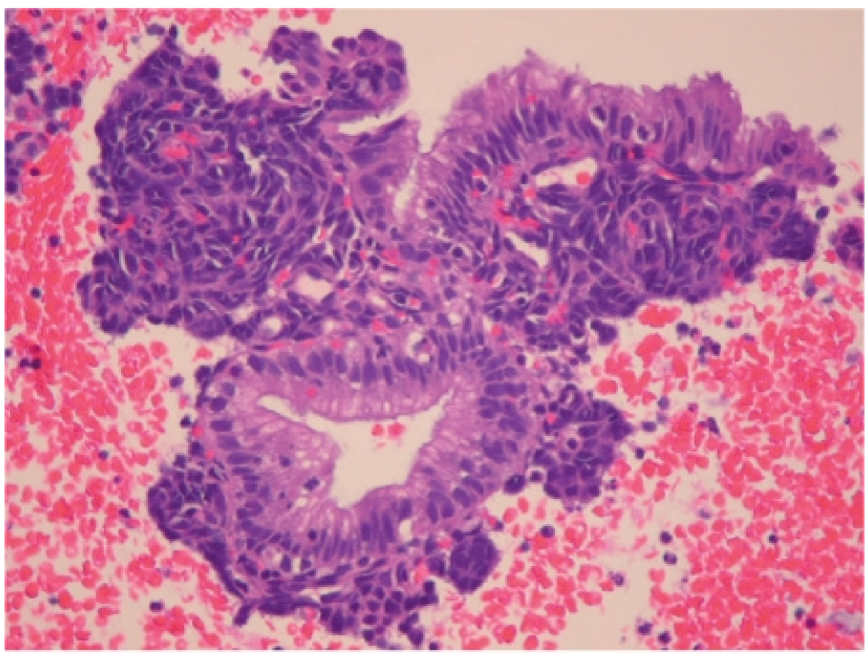
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



D

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photomicrograph illustrating endometrial changes during the menstrual cycle. **A.** Proliferative phase: straight to slightly coiled, tubular glands are lined by pseudostratified columnar epithelium with scattered mitoses. **B.** Early secretory phase: coiled glands with a slightly widened diameter are lined by simple columnar epithelium with clear subnuclear vacuoles. **C.** Late secretory phase: serrated, dilated glands with intraluminal secretion are lined by short columnar cells. **D.** Menstrual phase: fragmented endometrium with condensed stroma and glands with secretory vacuoles are seen in a background of blood. *(Courtesy of Dr. Kelley Carrick.)*

Following ovulation, the endometrium transforms into a secretory tissue. The period during and after transformation is defined as the *secretory phase* of the endometrium and correlates to the ovary's *luteal phase* . Glycogen-rich subnuclear vacuoles appear in cells lining the glands. Under further stimulation by progesterone, these vacuoles move from the glandular base toward the lumen and expel their contents. This secretory process peaks on approximately postovulatory day 6, coinciding with the day of implantation. Throughout the luteal phase, glands become increasingly tortuous, and the stroma becomes more edematous. In addition, spiral arteries that feed the endometrium increase their number and coiling.

If a blastocyst does not implant, then the corpus luteum is not maintained by placental hCG, progesterone levels drop, and endometrial glands begin to collapse. Polymorphonuclear leukocytes and monocytes from the nearby vasculature infiltrate the endometrium. The spiral arteries constrict leading to local ischemia, and lysosomes release proteolytic enzymes that accelerate tissue destruction. Prostaglandins (PGs), particularly prostaglandin F_2 , are present in the endometrium and likely contribute to arteriolar vasospasm. Prostaglandin F_2 also induces myometrial contractions, which may aid in expelling the endometrial tissue.

The entire endometrial functionalis layer is thought to exfoliate with menstruation, leaving only the basalis layer to provide cells for endometrial regeneration. However, in a number of reports, investigators have found large variations in the amount of tissue shed from different levels of the endometrium. Following menstruation, re-epithelialization of the desquamated endometrium is believed to be initiated within 2 to 3 days after the onset of menses and to be completed within 48 hours.

Regulation of Endometrial Tissue Degradation and Hemorrhage

Within the endometrium, a large number of proteins maintain a delicate balance between tissue integrity and the localized tissue destruction required for menstrual sloughing or for trophoblast invasion during implantation. Genes encoding these tissue proteins are believed to be regulated by cytokines, growth factors, and steroid hormones, although the details of this regulation are still incomplete.

Of these tissue proteins, tissue factor (TF) is a membrane- associated protein that activates the coagulation cascade on contact with blood. In addition, urokinase and tissue plasminogen activator (TPA) are both fibrinolytic, increasing the conversion of plasminogen to plasmin and activating tissue breakdown. TPA activity is blocked by plasminogen activator inhibitor-1 (PAI-1), also present in the endometrial stroma (Lockwood, 1993; Schatz, 1995). Importantly, matrix metalloproteinases (MMPs) are a family of enzymes with overlapping substrate specificities for collagens and other extracellular matrix components. The composition of the MMPs vary within the different endometrial tissues and during the menstrual cycle. Endogenous MMP inhibitors, called tissue inhibitors of matrix metalloproteinases (TIMPs), are also increased premenstrually and limit MMP degradative activity.

Endometrial Factors that Stimulate Vasoconstriction and Myometrial Contractility

Effective menstruation depends on appropriately timed endometrial vasoconstriction and myometrial contraction. Vasoconstriction produces ischemia, which leads to endometrial damage and subsequent menstrual sloughing. Within the endometrium, epithelial and stromal cells secrete endothelin-1, a member of a family of potent vasoconstrictors. Enkephalinase, which degrades endothelins, is expressed at its highest levels in the midsecretory endometrium (Head, 1993). However, in the late luteal phase, drops in serum progesterone levels lead to a loss of enkephalinase expression. This permits increased endothelin activity, which in turn provides a physiologic system inclined towards vasoconstriction.

In concert with endometrial sloughing, myometrial contractions control blood loss by compressing endometrial vasculature and expelling menstrual discharge.

A fall in serum progesterone decreases an enzyme that degrades prostaglandins. This allows increasing PGF_2 activity in the myometrium and triggers myometrial contractions (Casey, 1980).

Uterine Effects of Estrogens and Progestins

The expression of estrogen receptors and progesterone receptors in the endometrium is highly regulated across the menstrual cycle. This regulation of steroid receptor number provides an additional mechanism for controlling steroid effects on endometrial development and function.

Estrogen receptors are expressed in the nuclei of epithelial, stromal, and myometrial cells, and a peak concentration is seen during the proliferative phase. However, during the luteal phase, rising progesterone levels decrease estrogen receptor expression (Lessey, 1988).

Endometrial progesterone receptors peak at midcycle in response to rising estrogen levels. By midluteal phase, progesterone receptor expression in the endometrium is nearly absent, although expression remains strong in the stromal compartment (Lessey, 1988; Press, 1988).

The proliferation and differentiation of the uterine epithelium is under the control of estradiol, progesterone, and various growth factors. The importance of estrogens for endometrial development is emphasized by the documented increase in endometrial hyperplasia in women receiving unopposed estrogen therapy. Estrogen exerts its effects directly, through interaction with estrogen receptors and through induction of various growth factors including IGF-1, TGF-α, and epidermal growth factor (EGF) (Beato, 1989; Dickson, 1987). The effects of progesterone on endometrial growth vary among endometrial layers. Progesterone is clearly critical for the conversion of the functionalis layer from a proliferative to a secretory pattern. Moreover, progesterones also appear to promote cellular proliferation in the basalis layer.

Growth Factors and Cell Adhesion Molecules

A large number of growth factors and associated receptors have been identified in the endometrium (Table 15-7). Each of these factors has its own pattern of expression, and this complexity has made it difficult to determine which of the factors is most critical for endometrial function (Ohlsson, 1989; Sharkey, 1995).

Table 15-7 Endometrial Growth Factors and Their Function

Growth Factors	Suggested Function	Production Site
Transforming growth factor-β (TGF-β) family	Regulates extracellular matrix organization through regulation of TIMPs and PAI-1	Epithelial and stromal cells
Epidermal growth factor (EGF)	Stimulates stromal cell differentiation, regulates endometrial cell expression of integrins	Stromal and glandular cells
Insulin-like growth factors (IGF-I and IGF-II)	Promotes mitosis and differentiation in the endometrium	Endometrium, ovary, trophoblasts
IGF binding protein-1 (IGFBP-1)	Modulates trophoblast invasion	Decidualized stromal cells
Platelet-derived growth factor (PDGF)	Promotes angiogenesis, stimulates stromal cell proliferation	Stromal cells, activated platelets
Vascular endothelial growth factor (VEGF)	Modulates angiogenesis and vascular permeability	Glandular cells
Tumor necrosis factor-β (TNF-β)	Promotes mitogenic, angiogenic, inflammatory, and immunomodulatory effects	Endometrium, trophoblasts
Macrophage colony-stimulating factor (MCSF)	Stimulates monocyte maturation, regulates mature macrophage cell function	Endometrium, decidua, placenta
Leukemia inhibitory factor (LIF)	Promotes blastocyst implantation	Endometrium, blastocyst, placenta

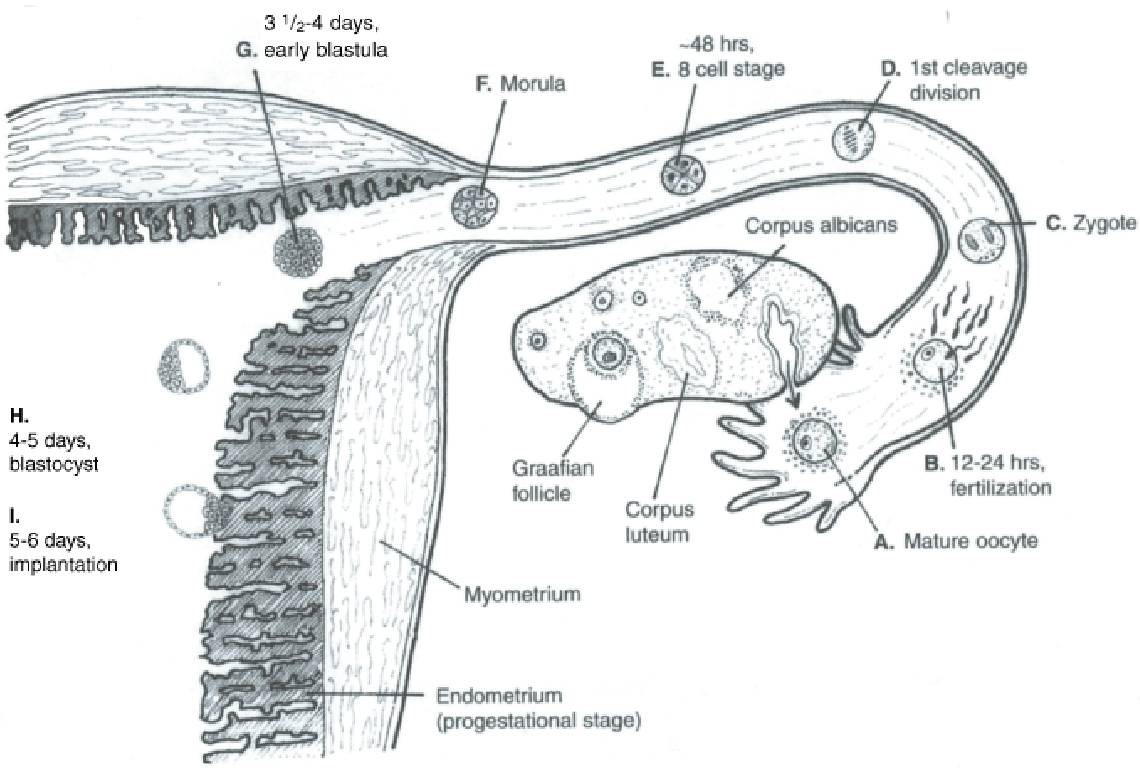
PAI-1 = plasminogen activator inhibitor-1; TIMP = tissue inhibitor of matrix metalloproteinase.

In addition to growth factors, cell adhesion molecules found within the endometrium play an important role in endometrial function. These molecules fall into four classes: the integrins, the cadherins, the selectins, and members of the immunoglobulin superfamily. Each has been implicated in endometrial regeneration and embryo implantation (Coutifaris, 1997).

Implantation Window

In the human, the embryo enters the uterine cavity 2 to 3 days after fertilization with implantation beginning approximately 4 days later (Fig. 15-25). Studies in humans and animal models have demonstrated that normal implantation and embryonic development require synchronous development of the endometrium and the embryo (Pope, 1988). The human blastocyst may have less stringent requirements for implantation than other species, as ectopic implantation occurs relatively frequently.

FIGURE 15-25



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Illustration depicts key points of conception: ovulation, fertilization, zygote transport through the fallopian tube, and implantation. *(From Barbieri, 1999, with permission.)*

Uterine receptivity can be defined as the temporal window of endometrial maturation during which trophectoderm attaches to the endometrial epithelial cells with subsequent invasion of the endometrial stroma. Based on a number of studies, the window of implantation in the human is relatively broad, extending from day 20 through day 24 of the menstrual cycle. Determination of this temporal window is critical, as only those factors expressed during this time can be considered putative markers or functional mediators of uterine receptivity.

Several investigators have attempted to correlate biochemical markers and ultrastructural features of the endometrium with the presence of uterine receptivity. Endometrial maturation is associated with loss of both surface microvilli and ciliated cells, as well as the development of cellular protrusions, called *pinopods,* on the apical surface of the endometrium. Specifically, the presence of

pinopods is considered to be an important morphologic marker of peri-implantation endometrium. Pinopod formation is known to be highly progesterone dependent (Yoshinaga, 1989).

Biochemical markers of uterine receptivity have included studies of mucin 1 (MUC1) and keratin sulfate. These transmembrane glycoproteins are significantly increased on the glandular cell surface during the peri-implantation period (Aoki, 1989). Integrins are also an intriguing putative marker for identification of the implantation window (Sueoka, 1997). However, to date no single integrin molecule has been determined to be the critical marker for identification of the implantation window.

Endometrial Dating and Luteal Phase Defect

In a classic study, Noyes and colleagues (1950) described a system for correlating the endometrial histologic appearance with menstrual cycle phase. With their system, a discrepancy of more than 2 days, termed a *luteal phase defect,* was linked to implantation failure and early pregnancy loss (Olive, 1991). Clinicians have traditionally chosen postovulatory days 10 to 12 of the menstrual cycle to obtain an endometrial biopsy. However, subsequent studies have suggested that endometrial sampling at the time of implantation (postovulation day 6) may be more accurate. Women diagnosed with luteal phase defects are typically treated with progesterone supplementation using natural progesterone products.

With time, it has become clear that there are multiple problems associated with endometrial dating. First, interpretation of the endometrial biopsies carries large intra- and interobserver variation. Second, the predictive value for an out-of-phase biopsy has proven to be lower than initially believed. Finally, it is unclear that progesterone supplementation improves pregnancy outcome. As a result, the endometrial biopsy has fallen from favor as an endometrial dating tool. However, as characterization of endometrial factors required for normal implantation moves forward, ultimately it may be possible to immunostain endometrial biopsy sections for these factors. This may produce more accurate biopsy interpretation.

ENDOCRINOLOGY OF PREGNANCY

Extensive endocrine changes occur in the maternal circulation during pregnancy because of altered maternal physiology as well as contributions by the placenta and fetus. A more detailed discussion of these changes can be found in *Williams Obstetrics,* 22nd edition (Cunningham, 2005).

Human Chorionic Gonadotropin

Human chorionic gonadotropin (hCG) is produced by placental trophoblasts and can be detected in serum as early as 7 to 9 days after the LH surge. Levels of hCG increase rapidly in early pregnancy, doubling approximately every 2 days. Levels of this peptide hormone peak at approximately 100,000 mIU/mL during the first trimester of pregnancy. This is followed by a relatively sharp decrease in the early second trimester and maintenance at lower levels throughout the remainder of pregnancy.

As noted earlier, hCG binds to LH/CG receptors on corpus luteum cells and stimulates steroidogenesis in the ovary. This peptide hormone is critical for corpus luteum steroid production during early pregnancy before the placenta attains adequate steroidogenic capability to maintain endometrial integrity and uterine quiescence. The transfer in production of estrogens and progesterone from the ovary to the placenta is often called the "luteal-placental shift".

As the placenta is the primary source for hCG production, measurement of plasma hCG levels has proven to be an effective screening tool for pregnancies with altered placental mass or function. Relatively elevated levels of hCG are observed with mutifetal gestation or a fetus with Down syndrome. Lower hCG levels are observed in cases of poor placentation, as occurs in ectopic pregnancy or spontaneous miscarriage. Serial hCG measurements can be very helpful to monitor these latter conditions, as the doubling time is relatively reliable (see Chap. 7, Serum β-HCG Measurements).

Markedly abnormal elevations in hCG levels are most often observed in the presence of gestational trophoblastic disease, including hydatidiform mole and choriocarcinoma (see Chap. 37). As noted previously, hCG and thyroid-stimulating hormone (TSH) share a common α-subunit and related β-subunits. Due to this structural similarity, hCG can bind to and activate TSH receptors in the thyroid gland, explaining the association of molar pregnancy with hyperthyroidism.

In addition, hCG can be a useful tumor marker for nontrophoblastic neoplasias. Ectopic (nonplacental) production of hCG, either the intact dimer or the α-subunit, is frequently associated with germ cell tumors and has been reported for a variety of tumors

arising from the mucosal epithelium of the cervix, bladder, lung, and nasopharynx (see Chap. 36, Laboratory Testing). It has been postulated that hCG inhibits apoptosis in these tumors, thereby allowing rapid growth (Iles, 2007).

Hypothalamic and Pituitary Peptide Hormones

The placenta produces a remarkable number of peptide hormones. Many of these are more commonly thought of as hypothalamic or pituitary in origin. For example, the placenta secretes thyrotropin-releasing hormone (TRH), gonadotropin-releasing hormone (GnRH), corticotropin-releasing hormone (CRH), growth hormoneâ€œreleasing hormone (GHRH), and somatostatin. Pituitary-like peptides include human chorionic gonadotropin (hCG), adrenocorticotropin hormone (ACTH), human placental lactogen (hPL), and human growth hormone variant (hGH-v). The placenta also is notable for its production of inhibins, activins, relaxin, and atrial natriuretic peptide.

Placental Steroids

LUTEAL-PLACENTAL SHIFT

The corpus luteum is the major source of steroid production in early pregnancy. By the seventh week of gestation, approximately 50 percent of estrogen in the maternal circulation is produced in the placenta (Siiteri, 1966). Removal of the corpus luteum will result in miscarriage before the switch to placental steroid production. Using a conservative approach, progesterone supplementation should be considered in any woman who has surgical removal of the corpus luteum before 10 weeks of gestation, with supplementation continued at least to this time (see Chap. 6, Maternal Surgery).

PROGESTERONE

Placental progesterone is synthesized from cholesterol primarily derived from maternal circulation. Cholesterol is initially converted to pregnenolone, which next is converted to progesterone by 3β-hydroxysteroid dehydrogenase. Progesterone is secreted continuously into the maternal circulation rather than stored, as occurs for peptide products. Maternal progesterone serum levels increase from approximately 25 ng/mL during the midluteal phase to 150 ng/mL at term. Progesterone has been postulated to be the critical mediator of uterine quiescence during pregnancy, possibly via inhibition of prostaglandin synthesis. Progesterone is also a potent immunomodulatory agent that may block immune rejection of the developing fetus.

ESTRIOL

The placenta lacks the steroidogenic enzyme CYP17, which is required for converting C21 steroids, including progesterone, into C19 androgens. Therefore, placental estrogen production is dependent on precursors provided by other systems. While progesterone production is dependent on maternal precursors, estrogen production is dependent on precursors from the fetal adrenal gland.

The fetal adrenal gland is nearly as large as the fetal kidney, and therefore is proportionally enlarged relative to the adult adrenal gland. The fetal adrenal cortex produces DHEAS, which is subsequently hydroxylated to form 16α-hydroxy-DHEAS in the fetal liver. The high levels of aromatase activity in the placenta convert 16α-hydroxy-DHEAS to estriol, explaining the high circulating levels of this steroid during pregnancy (Siiteri, 1966). As with progesterone, most placental estrogen enters the maternal compartment.

Estriol is considered the "pregnancy estrogen", as it is only expressed at high levels at this time. Nevertheless, it should be appreciated that the more potent estrogen, estradiol, is produced in equal or slightly higher concentrations and may be responsible for observed estrogenic effects.

STEROID PRODUCTION RELATED TO FETAL WELL BEING

It has been appreciated for many decades that measurement of urinary estriol can be used as a marker for fetal health. Estrogen levels are markedly blunted in patients making low levels of androgen precursors, such as occurs in anencephaly, adrenal hypoplasia, or fetal demise. Serum estriol is now used in the second trimester as part of the triple screen and quadruple screen to look for Down syndrome and neural-tube defects, among other fetal anomalies.

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AMENORRHEA: INTRODUCTION

Evaluation and management of a patient with amenorrhea is a common practice in gynecology, and the prevalence of pathologic amenorrhea ranges from 3 to 4 percent in reproductive-aged populations (Bachmann, 1982; Pettersson, 1973). Amenorrhea is diagnosed in a female who has not menstruated: (1) by age 13 years and who lacks other evidence of pubertal development; (2) by age 15, even in the presence of other pubertal signs; or (3) for a length of time equivalent to a total of three previous cycle intervals or 6 months. Although amenorrhea has classically been defined as *primary* (no prior menses) or *secondary* (cessation of menses), this distinction may lead to diagnostic error and should be avoided.

In some circumstances, it is reasonable to initiate an evaluation despite the absence of these strict criteria. Examples include a patient with the stigmata of Turner syndrome, obvious virilization, or a history of uterine curettage. An evaluation for delayed puberty should also be considered before the ages listed if a patient or her parents are concerned.

Although the list of possible etiologies is extensive, most causes will fall into a limited number of categories (Tables 16-1 and 16-2). Of course, amenorrhea is a normal state prior to puberty, during pregnancy and lactation, and following the menopause.

Table 16-1 Primary Amenorrhea: Frequency of Etiologies

Presentation	Frequency (%)
Hypergonadotropic hypogonadism	43
45,X and variants	27
46,XX	14
46,XY	2
Eugonadism	30
MÃ¼llerian agenesis	15
Vaginal septum	3
Imperforate hymen	1
AIS	1
PCOS	7
CAH	1
Cushing and thyroid disease	2
Low FSH without breast development	27

Constitutional delay	14
GnRH deficiency	5
Other CNS disease	1
Pituitary disease	5
Eating disorders, stress	2

AIS = androgen insensitivity syndrome; CAH = congenital adrenal hyperplasia; CNS = central nervous system; FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; PCOS = polycystic ovarian syndrome.

Adapted from Reindollar, 1981, with permission.

Table 16-2 Secondary Amenorrhea: Frequency of Etiologies

Etiology	Frequency (%)
Low or normal FSH level: various	67.5
Eating disorders, stress	15.5
Nonspecific hypothalamic	18
Chronic anovulation (PCOS)	28
Hypothyroidism	1.5
Cushing syndrome	1
Pituitary tumor/empty sella	2
Sheehan syndrome	1.5
High FSH level: gonadal failure	10.5
46,XX	10
Abnormal karyotype	0.5
High prolactin level	13
Anatomic	7
Asherman syndrome	7
Hyperandrogenic states	2
Late-onset CAH	0.5
Ovarian tumor	1
Undiagnosed	0.5

CAH = congenital adrenal hyperplasia; FSH = follicle-stimulating hormone; PCOS = polycystic ovarian syndrome.

Adapted from Reindollar, 1986, with permission.

NORMAL MENSTRUAL CYCLE

A differential diagnosis for amenorrhea can be developed based on requirements for normal menses. Generation of a cyclic, controlled pattern of uterine bleeding requires precise temporal and quantitative regulation of a number of reproductive hormones.

First, the hypothalamic-pituitary-ovarian axis must be functional. The hypothalamus releases pulses of gonadotropin-releasing hormone (GnRH) into the portal circulation at defined frequencies and amplitude. Gonadotropin-releasing hormone stimulates the synthesis and secretion of the gonadotropins, that is, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), by the gonadotrope cells of the anterior pituitary gland. These gonadotropins enter the peripheral circulation and act on the ovary to stimulate both follicular development and ovarian hormone production. These ovarian hormones include the steroid hormones (estrogen, progesterone, and androgens), as well as the peptide hormone inhibin. As suggested by its name, inhibin blocks FSH synthesis and secretion. Gonadal steroids are inhibitory in both the pituitary and the hypothalamus. Development of a mature follicle results in a rapid rise in estrogen levels, which acts positively at the pituitary to generate a surge in LH release. The mechanism by which this previously negative estrogen feedback switches to positive feedback is unknown. In addition to LH release, circulating estrogens stimulate the development of a thickened, proliferative, endometrial lining.

Following ovulation, LH stimulates luteinization of the follicular granulosa cells and surrounding theca with the formation of the corpus luteum. The corpus luteum continues to produce estrogen, but also secretes high levels of progesterone. Progesterone converts the endometrium to a secretory pattern. If pregnancy occurs, the corpus luteum is "rescued" by human chorionic gonadotropin (hCG) secreted from early trophoblastic cells. If pregnancy does not occur, then progesterone and estrogen secretion ceases, the corpus luteum regresses, and endometrial sloughing ensues. The pattern of this "progesterone withdrawal bleed" will vary in duration and blood loss between women, but should be relatively constant across cycles for each individual.

Menses can be absent even in the presence of normal cyclic hormonal changes due to the presence of anatomic abnormalities. The endometrium must be able to respond normally to hormonal stimulation, and the cervix, vagina, and introitus must be present and patent.

CLASSIFICATION SYSTEM

Numerous classification systems for the diagnosis of amenorrhea have been developed, and all have their strengths and weaknesses. One useful scheme is outlined in Table 16-3. This system divides the causes of amenorrhea into anatomic versus hormonal etiologies with further division into inherited versus acquired disorders.

Table 16-3 Classification Scheme for Amenorrhea
Anatomic
Inherited
MÃ¼llerian agenesis (partial or complete)
Vaginal septum
Cervical atresia
Imperforate hymen
Labial fusion
Acquired

Intrauterine synechiae (Asherman syndrome)
Dilatation and curettage
Infection (tuberculosis)
Cervical stenosis
Hormonal/endocrinologic
Hypergonadotropic hypogonadism
Premature ovarian failure (POF)
Inherited
Chromosomal (gonadal dysgenesis)
Single gene disorders
Acquired
Infectious
Autoimmune
Iatrogenic
Environmental
Idiopathic
Hypogonadotropic hypogonadism
Disorders of the hypothalamus
Inherited
Idiopathic hypogonadotropic hypogonadism (IHH)
Kallmann syndrome
Acquired
Hypothalamic amenorrhea ("functional")
Eating disorders
Excessive exercise
Stress
Destructive processes
Tumor

Radiation
Infection
Infiltrative disease
Pseudocyesis
Disorders of the anterior pituitary gland
Inherited
Pituitary hypoplasia
Acquired
Adenoma
Prolactinoma
Destructive processes
Macroadenoma
Metastases
Radiation
Trauma
Infarction (Sheehan syndrome)
Infiltrative disease
Chronic disease
End-stage kidney disease
Liver disease
Malignancy
Acquired immunodeficiency syndrome
Malabsorption syndromes
Eugonadotropic amenorrhea
Inherited
Polycystic ovarian syndrome
Late-onset congenital adrenal hyperplasia
Ovarian tumors (steroid-producing)

Acquired
Hyperprolactinemia
Thyroid disease
Cushing syndrome
Acromegaly

As described above, normal menses requires adequate ovarian production of steroid hormones. Decreased ovarian function (hypogonadism) may result either from a lack of stimulation by the gonadotropins (*hypo* gonadotropic hypogonadism) or from primary failure of the ovary (*hyper* gonadotropic hypogonadism) (Table 16-4).

Table 16-4 Categories of Amenorrhea Based on Gonadotropin and Estrogen and Levels

Type of Hypogonadism	LH/FSH	Estrogen	Primary Defect
Hyper gonadotropic	High	Low	Ovary
Hypo gonadotropic	Low	High	Hypothalamus/pituitary
Eu gonadotropic	Normal[a]	Normal[a]	Varied

[a] Generally in normal range, but lack cyclicity.

FSH = follicle-stimulating hormone; LH = luteinizing hormone.

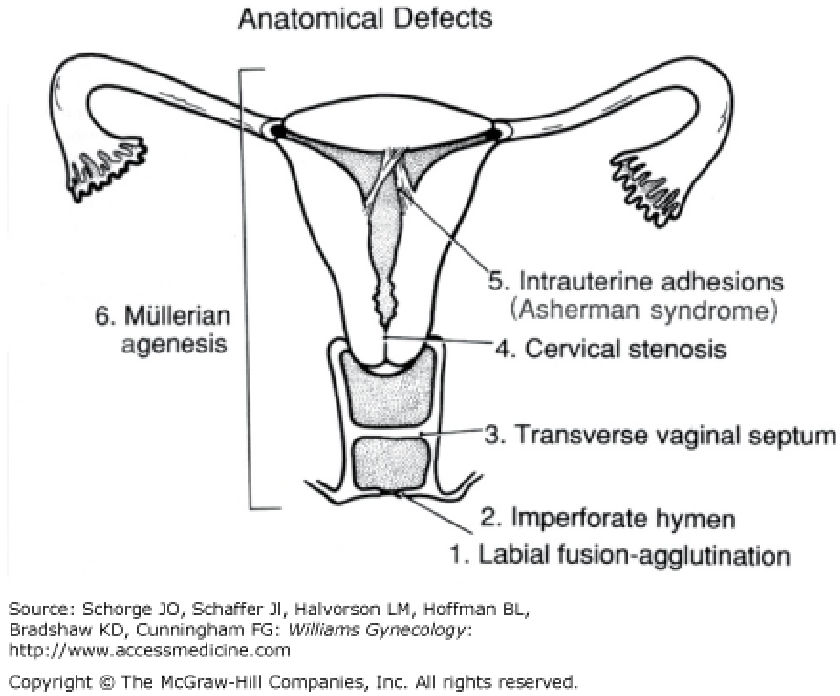
ANATOMIC DISORDERS

Anatomic abnormalities that may present as amenorrhea can broadly be viewed as either inherited or acquired disorders of the outflow tract (uterus, cervix, vagina, and introitus) (see Chap. 18, Description and Patient Presentation).

Inherited

These are a frequent cause of amenorrhea in adolescents, and pelvic anatomy is abnormal in approximately 15 percent of women with primary amenorrhea (American Society for Reproductive Medicine, 2006). Figure 16-1 depicts the range of anatomic defects that may present with amenorrhea.

FIGURE 16-1



Drawing of vagina, uterus, and fallopian tubes demonstrating defects at various sites. *(From Bradshaw, 2005, with permission.)*

OUTFLOW TRACT OBSTRUCTION

Beginning at the caudal end of the female genital tract, labial agglutination or fusion is often associated with disorders of sexual development, particularly female pseudohermaphroditism due to excess androgen exposure of a 46,XX female fetus in utero. These androgens may be due to fetal congenital adrenal hyperplasia (CAH) or may be derived from maternal circulation, such as develops with a luteoma of pregnancy.

Amenorrhea will be observed in the presence of an imperforate hymen (1 in 2,000 women), a transverse vaginal septum (1 in 70,000 women), or isolated atresia of the vagina or cervix (see Figs. 18-5 and 18-10) (Banerjee, 1999; Parazzini, 1990; Reid, 2000). Patients with these anomalies have a 46,XX karyotype, female secondary sexual characteristics, and normal ovarian function. Therefore, the amount of uterine bleeding is normal, but its typical path for egress is obstructed or absent. These patients may note moliminal symptoms, such as breast tenderness, food cravings, and mood changes, which are attributable to elevated progesterone levels. In addition, accumulation of menstrual blood behind an obstruction frequently results in cyclic abdominal pain or palpable abdominal mass. In women with outflow tract obstruction, an increase in retrograde menstruation may lead to development of endometriosis with associated complications such as chronic pain and infertility.

MÃ¼LLERIAN DEFECTS

During embryonic development, the mÃ¼llerian ducts give rise to the upper vagina, cervix, uterine corpus, and fallopian tubes (Fig. 18-1). MÃ¼llerian agenesis may be partial or complete. Accordingly, amenorrhea may result from outflow obstruction or from a lack of endometrium in cases involving uterine agenesis. In complete mÃ¼llerian agenesis, often called Mayer-Rokitansky-KÃ¼ster-Hauser syndrome, patients fail to develop any mÃ¼llerian structures and on examination are found to have only a vaginal dimple. In a report from Finland, approximately 1 in 5,000 newborn females were identified with this disorder, thus it ranks second only to gonadal dysgenesis as a cause of primary amenorrhea (Aittomaki, 2001; Reindollar, 1981).

The presentation of complete mÃ¼llerian agenesis may be confused with androgen insensitivity syndrome. In the latter condition, a patient has a 46,XY karyotype and functioning testes, however, the body cannot respond to testosterone due to mutations in the androgen receptor. These two syndromes are compared in Table 16-5 and discussed further in Chapter 18, Pathophysiology.

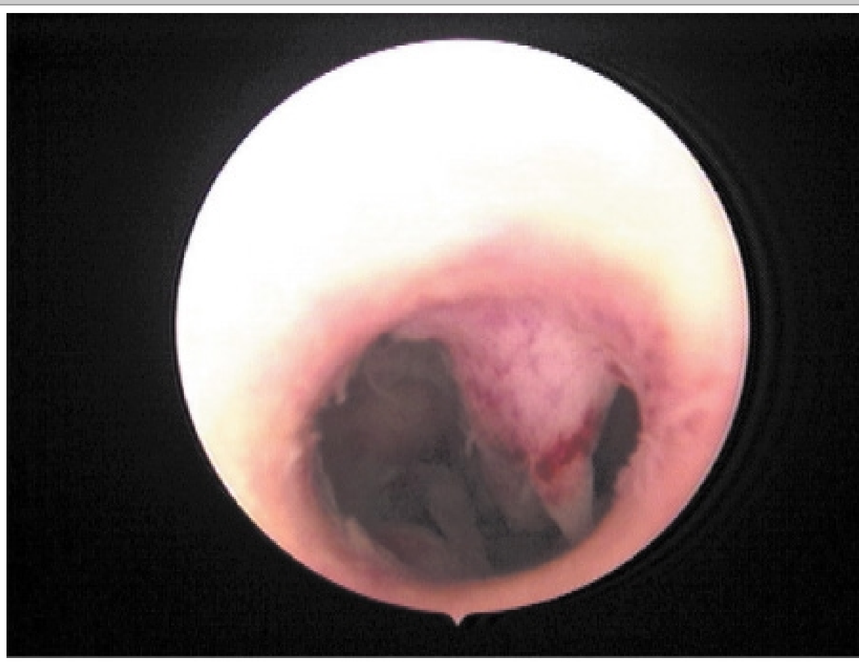
Table 16-5 Comparison of MÃ¼llerian Agenesis and Androgen Insensitivity Syndrome		
Presentation	**MÃ¼llerian Agenesis**	**Androgen Insensitivity**
Inheritance pattern	Sporadic	X-linked recessive
Karyotype	46,XX	46,XY
Breast development	Yes	Yes
Axillary and pubic hair	Yes	No
Uterus	No	No
Gonad	Ovary	Testis
Testosterone	Female levels	Male levels
Associated anomalies	Yes	No

Acquired

Other abnormalities of the uterus that cause amenorrhea include obstruction due to stenosis of the cervix. This may result from conization, electrosurgery, or cryosurgery used to treat cervical dysplasia.

Amenorrhea may also be observed with extensive intrauterine scarring. The presence of this scar tissue, also called uterine synechiae, is termed Asherman syndrome (Fig. 16-2). In less severe cases, patients may present with hypomenorrhea or recurrent pregnancy loss.

FIGURE 16-2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Hysteroscopic photograph displays intrauterine adhesions found with Asherman syndrome. *(Courtesy of Dr. Kevin Doody.)*

The endometrium is divided into a functional layer, which lines the endometrial cavity, and a basal layer, which regenerates the functional layer with each menstrual cycle. Destruction of the basal endometrium prevents endometrial thickening in response to ovarian steroids. Therefore, no tissue is produced and subsequently passed when steroid hormone levels fall at the end of the luteal phase.

Endometrial damage may follow vigorous curettage, usually in association with postpartum hemorrhage, miscarriage, or therapeutic abortion complicated by infection. Damage may also result from other uterine surgery including metroplasty, myomectomy, or cesarean delivery, or from infection related to an intrauterine device. Although rare in the United States, tuberculous endometritis is a relatively common cause of Asherman syndrome in developing countries (Buttram, 1977; Klein, 1973). If they are surgically treated and achieve pregnancy, these patients must be monitored carefully because of the increased risk of uterine rupture or placenta accreta (Capella-Allouc, 1999; Deaton, 1989; Fernandez, 2006). Further discussion of Asherman syndrome is found in Chapter 18, Asherman Syndrome. Surgical lysis of these intrauterine adhesions is described in Section 41-41, Lysis of Intrauterine Adhesions.

ENDOCRINE DISORDERS

Hypergonadotropic Hypogonadism (Premature Ovarian Failure)

The term *hypergonadotropic hypogonadism* refers to any process in which ovarian function is decreased or absent (hypogonadism). Due to a lack of negative feedback, the gonadotropins, LH and FSH, have increased levels (hypergonadotropic). This category of disorders implies primary dysfunction at the level of the ovary, rather than centrally at the hypothalamus or pituitary. This process can also be termed *premature menopause* or *premature ovarian failure* (POF). The latter term is preferable, as it better describes the pathophysiology of this condition.

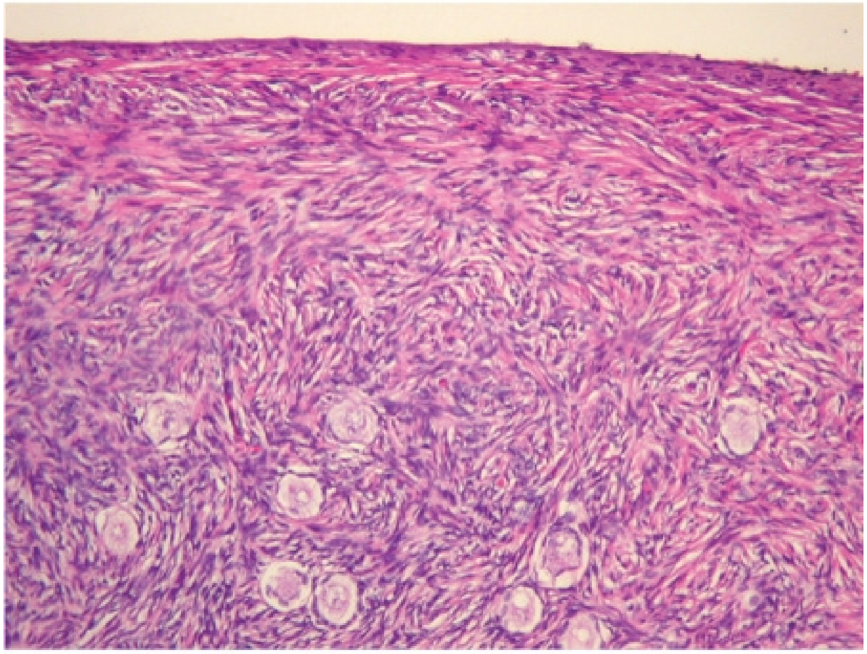
Premature ovarian failure is defined as loss of oocytes and the surrounding support cells prior to age 40 years. The diagnosis is determined by two serum FSH levels greater than 40 mIU/mL that are obtained at least 1 month apart. This definition distinguishes POF from the physiologic loss of ovarian function, which occurs with normal menopause. The incidence of premature ovarian failure has been estimated at 1 in 1,000 women less than 30 years, and 1 in 100 women less than 40 years (Coulam, 1986). A careful evaluation is mandatory (Premature Ovarian Failure). Nevertheless, in most cases, the etiology of POF is not determined.

HERITABLE DISORDERS

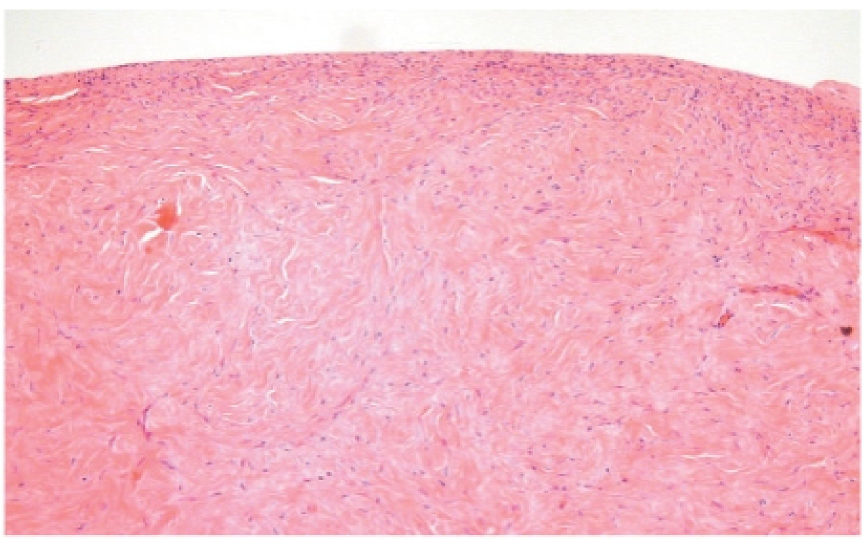
Chromosomal Defects

Gonadal dysgenesis is the most frequent cause of POF. In this disorder, although a normal complement of germ cells is present in the early fetal ovary, oocytes undergo accelerated atresia, and the ovary is replaced by a fibrous streak (Fig. 16-3) (Simpson, 1975; Singh, 1966). Individuals with gonadal dysgenesis may present with a variety of clinical features and can be divided into two broad groups based on whether the patient's karyotype is normal or abnormal (Schlessinger, 2002).

FIGURE 16-3



A



B

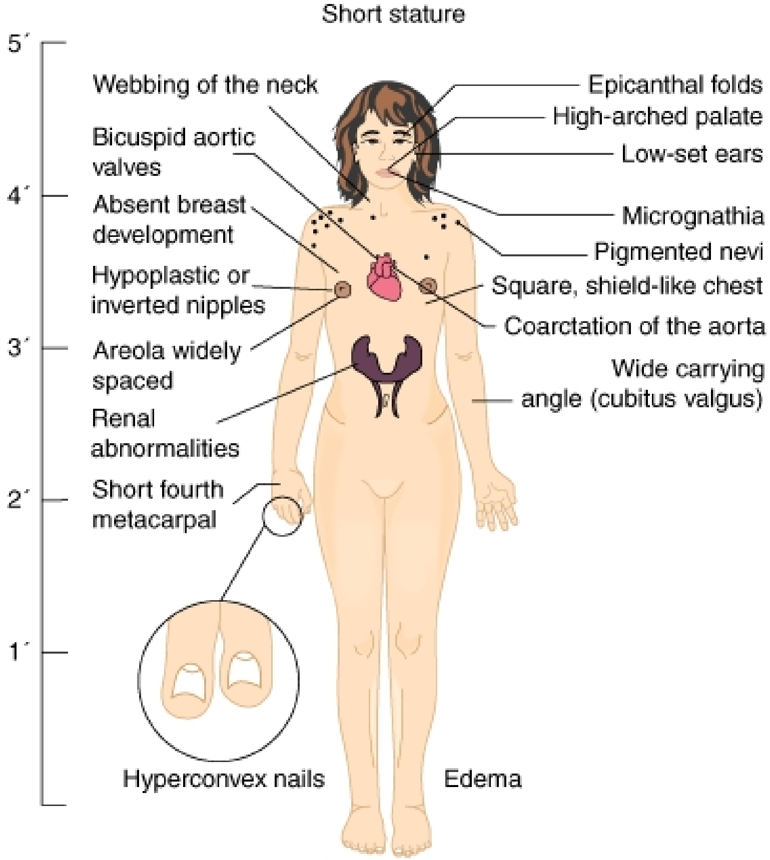
Photomicrographs of histologic samples. **A.** Normal premenopausal ovarian cortex with multiple primordial follicles. (Courtesy of Dr. Kelley Carrick.) **B.** Ovary from a woman with gonadal dysgenesis. Streak ovary showing ovarian-type stroma with no primordial follicles. *(Courtesy of Dr. Raheela Ashfaq.)*

Abnormal Karyotype

Deletion of genetic material from an X chromosome accounts for about two thirds of gonadal dysgenesis (Devi, 1998; Tho, 1981). These patients are said to have Turner syndrome. A 45,X karyotype is found in about half of these patients, most of whom have associated somatic defects including short stature, webbed neck, low hairline, shield-shaped chest, and cardiovascular defects (Fig. 16-4 and Table 16-6) (Turner, 1972).

Table 16-6 Characteristic Findings in Women with Turner Syndrome
Height 142â€"147 cm
Micrognathia
Epicanthal folds
Low-set ears
Sensorineural hearing loss
Otitis media leading to conductive loss
High-arched palate
Webbing of the neck
Chest square and shield-like
Lack of breast development
Areola widely spaced
Coarctation of the aorta
Short fourth metacarpal
Cubitus valgus
Renal abnormalities
Autoimmune disorders
Autoimmune thyroiditis
Diabetes mellitus

FIGURE 16-4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Drawing illustrating the classical phenotypic characteristics of women with Turner syndrome. Table 16-6 lists these physical traits.

The remaining patients with gonadal agenesis and identifiable abnormalities of the X chromosome have chromosomal mosaicism with or without associated structural abnormalities of the X chromosome. In these cases, the most common form of mosaicism is a 45,X/46,XX karyotype (Tho, 1981). Short stature and somatic abnormalities are most closely linked to deletions in the short arm of the X chromosome (Xp). Patients with deletion of the long arm of the X chromosome frequently have normal stature or may even have a eunuchoid body type. The low levels of estrogens in these patients results in delayed closure of the epiphyses of the long bones, resulting in long arms and legs relative to the torso. This appearance is termed a *eunuchoid habitus* (Baughman, 1968; Hsu, 1970).

Approximately 90 percent of individuals with gonadal dysgenesis due to loss of X genetic material never have menstrual bleeding. The remaining 10 percent have sufficient residual follicles to experience menses, and rarely may achieve pregnancy. However, the menstrual and reproductive lives of such individuals are invariably brief (Kaneko, 1990; Simpson, 1975; Tho, 1981).

In cases of gonadal agenesis, chromosomal mosaicism may also include the presence of a Y chromosome, such as 45,X/46,XY. Thus, chromosomal analysis should be performed in all cases of amenorrhea associated with POF, particularly before age 30. The presence of a Y chromosome cannot be determined clinically, as only a minority of patients will demonstrate signs of androgen excess. A streak gonad should be removed if Y chromosomal material is found, as nearly 25 percent of these patients will develop a malignant germ cell tumor (see Chap. 36) (Manuel, 1976; Simpson, 1975; Troche, 1986). In many cases, this can be accomplished laparoscopically (Wilson, 1992).

Normal Karyotype

The remaining one third of patients with gonadal dysgenesis will have a normal karyotype (46,XX or 46,XY) and are said to have "pure" gonadal dysgenesis. Patients with a 46,XY genotype are phenotypically female due to the lack of secretion of testosterone and mÃ¼llerian inhibiting substance by the dysgenetic testes. The etiology of the gonadal failure in both genetically male and female patients is poorly understood, but is likely due to single gene defects or destruction of gonadal tissue in utero, perhaps by infection or toxins.

Specific Genetic Defects

In addition to the chromosomal abnormalities described above, rarely patients may experience POF due to mutations in single genes. For example, mutation in the *CYP17* gene results in decreased 17-α-hydroxylase and 17,20-lyase activity, thereby preventing the production of cortisol, androgens, and estrogens (see Fig. 15-13). These patients have sexual infantilism and primary amenorrhea due to a lack of estrogen secretion. *Sexual infantilism* describes patients with a lack of breast development, lack of pubic and axillary hair, and a small uterus. Mutations in the *CYP17* gene also lead to an increase in adrenocorticotropin hormone (ACTH) secretion thereby stimulating mineralocorticoid secretion. This in turn leads to the development of hypokalemia and hypertension (Goldsmith, 1967).

Mutations in the LH and FSH receptors have also been reported in those with POF. These mutations prevent normal response to circulating gonadotropins, a condition termed *resistant ovary syndrome* (Aittomaki, 1995; Kim, 1974).

Galactosemia is a rare cause of POF. Inherited as an autosomal recessive disorder, this condition leads to abnormal galactose metabolism due to a deficiency of galactose-1-phosphate uridyl transferase, encoded by the *GALT* gene. Galactose metabolites are believed to have a direct toxic effect on germ cells. As a result, heterozygote carriers of this disorder may have suboptimal ovarian function. Galactosemia is frequently diagnosed during newborn screening programs or pediatric evaluation for associated growth and developmental impairment, and long before a patient would present to a gynecologist (Kaufman, 1981; Levy, 1984; Robinson, 1984).

ACQUIRED ABNORMALITIES

Hypergonadotropic hypogonadism can be acquired via infection, autoimmune disease, medical treatments, or from other causes. Infectious causes of POF are relatively rare and poorly understood, with mumps oophoritis most frequently reported (Morrison, 1975).

Autoimmune Disease

Autoimmune disorders are estimated to account for 40 percent of POF cases (Hoek, 1997; LaBarbera, 1988). Ovarian failure may be one component of polyglandular failure together with hypothyroidism, adrenal insufficiency, or other autoimmune disorders such as systemic lupus erythematosus. Although a number of anti-ovarian antibodies have been characterized, there is currently no validated serum antibody marker to assist in the diagnosis of autoimmune POF (American Society for Reproductive Medicine, 2006). Therefore, lacking a firm diagnosis, all women with POF should be evaluated for the presence of other autoimmune disorders (Premature Ovarian Failure). In addition to adrenal and thyroid disease, POF has been associated with myasthenia gravis, idiopathic thrombocytopenic purpura, rheumatoid arthritis, vitiligo, and autoimmune hemolytic anemia (Belvisi, 1993; de Moraes, 1972; Kalantaridou, 1998; Mignot, 1989).

Iatrogenic Causes

Iatrogenic ovarian failure is a relatively common presentation. This group includes patients who have undergone surgical complete removal or excision of a significant portion of the ovaries. A patient may experience amenorrhea following pelvic radiation for malignancies such as Hodgkin's disease. Preventively, ovaries should be surgically repositioned (oophoropexy) if possible, out of the anticipated radiation field prior to therapy (Horning, 1981).

Ovarian failure may also follow chemotherapy for treatment of malignancies or severe autoimmune diseases (Marhhom, 2007). Alkylating agents are believed to be particularly damaging to ovarian function. To minimize the resulting oocyte depletion, use of GnRH agonists or antagonists concurrent or prior to chemotherapy may be beneficial (Giuseppe, 2007; Pereyra, 2001; Somers,

2005).

A number of mechanisms by which GnRH analogs exert their protective effects have been proposed. These medications decrease ovarian blood flow, and thereby, decrease exposure of the ovaries to chemotherapeutic agents (Blumenfeld, 2003). Dividing cells are known to be more sensitive than cells at rest to the cytotoxic effects of these agents. Therefore, it has been suggested that inhibition of the pituitary-gonadal axis may protect the germinal epithelium by inhibiting oogenesis. Alternatively, as GnRH receptors have been identified in the ovary, GnRH agonists may act directly at the ovary to decrease granulosa cell metabolism (Peng, 1994). However, this explanation is not totally satisfactory, as the early stages of oogenesis occur independently of gonadotropin stimulation.

The chance of developing ovarian failure is correlated with increasing radiation and chemotherapeutic dose. Permanent ovarian failure almost invariably results from a dose of more than 8 Gy (800 rads) applied directly to the ovary (Ash, 1980). Patient age is also a significant factor, and younger patients are less likely to develop failure and more likely to regain ovarian function over time (Gradishar, 1989; Tham, 2007; Wallace, 1989).

A wide variety of environmental toxins have a clear detrimental effect on follicular health. These include cigarette smoking, heavy metals, solvents, pesticides, and industrial chemicals (Jick, 1977; Mlynarcikova, 2005; Sharara, 1998).

Hypogonadotropic Hypogonadism

The term *hypogonadotropic hypogonadism* implies that the primary abnormality lies in the hypothalamic-pituitary axis. A decrease in gonadotropin stimulation of the ovaries leads to loss of ovarian hormone production. Generally in these patients, LH and FSH levels, although low, will still be in the detectable range (<5 mIU/mL). However, levels may be undetectable in patients with complete absence of hypothalamic stimulation, such as occurs in Kallmann syndrome. In addition, absent pituitary function due to abnormal development or severe pituitary damage may lead to similarly low levels. The group of hypogonadotropic hypogonadism disorders may be viewed as a continuum with perturbations leading to luteal dysfunction, oligomenorrhea, and in the most severe presentation, amenorrhea.

DISORDERS OF THE HYPOTHALAMUS

Inherited Abnormalities

Inherited hypothalamic abnormalities primarily consist of those patients with idiopathic hypogonadotropic hypogonadism (IHH). Of these patients, a subset has associated defects in the ability to smell (hyposmia or anosmia) and are said to have Kallmann syndrome. This syndrome can be inherited as an X-linked, autosomal dominant or autosomal recessive disorder (Cadman, 2006; Layman, 1999; Waldstreicher, 1996). The X-linked form follows mutation in the *KAl1* gene on the X chromosome short arm, and is an uncommon cause of Kallman syndrome (Bhagavath, 2007). Expressed during fetal development, this gene encodes an adhesion protein, named anosmin-1, which is critical for normal migration of both GnRH and olfactory neurons from the olfactory placode to the hypothalamus and olfactory cortex, respectively (Franco, 1991; Soussi-Yanicostas, 1996). The autosomal dominant form of Kallmann syndrome accounts for about 10 percent of cases and is now known to be due to mutation in the gene which encodes fibroblastic growth factor receptor 1 (FGFR1) (Bhagavath, 2007).

Based on postmortem analyses, Kallmann patients have a normal complement of GnRH neurons, however, these neurons fail to migrate and remain near the nasal epithelium (Quinton, 1997). As a result, locally secreted GnRH fails to stimulate gonadotropin secretion by the anterior pituitary gland. Marked decreases in ovarian estrogen production result in a lack of breast development or menstrual cycles.

Kallmann syndrome is also associated with midline facial anomalies such as cleft palate, unilateral renal agenesis, cerebellar ataxia, epilepsy, neurosensory hearing loss, and synkinesis (mirror movements of the hands) (Winters, 1992; Zenaty, 2006). Kallmann syndrome can be distinguished from idiopathic hypogonadotropic hypogonadism (IHH) by olfactory testing. This can be done easily in the office with strong odorants such as ground coffee or perfume. Interestingly, many of these patients are unaware of their deficit.

ACQUIRED HYPOTHALAMIC DYSFUNCTION

Functional Disorders or Hypothalamic Amenorrhea

Inherited hypothalamic abnormalities are markedly less common than acquired deficiencies. Most frequently, gonadotropin deficiency leading to chronic anovulation is believed to arise from functional disorders of the hypothalamus or higher brain centers. Also called *hypothalamic amenorrhea* , this diagnosis encompasses three main categories: eating disorders, extreme exercise, and stress. From a teleologic perspective, amenorrhea in time of starvation or extreme stress can be seen as a mechanism to prevent pregnancy at a time in which resources are suboptimal for supporting a child. Each woman appears to have her own hypothalamic "set-point" or sensitivity to environmental factors. For example, individual women can tolerate significantly different amounts of stress without developing amenorrhea.

Eating Disorders

The eating disorders, anorexia nervosa and bulimia, can both result in amenorrhea. Anorexia nervosa is associated with severe caloric restriction, weight loss, self-induced vomiting, excess use of laxatives, and compulsive exercise (see Chap. 13, Eating Disorders). Weight loss is generally less severe in bulimic women, who eat in binges then purge to maintain weight.

Hypothalamic dysfunction is severe in anorexia and may affect other hypothalamic-pituitary axes in addition to the reproductive axis. Amenorrhea in anorexia nervosa can precede, follow, or appear coincidentally with weight loss. In addition, even with return to normal weight, not all women with anorexia will regain normal menstrual function.

Exercise-Induced Amenorrhea

This is most commonly seen in women whose exercise regimen is associated with significant loss of fat, such as ballet, gymnastics, and long-distance running (De Souza, 1991; Frisch, 1980). In those women who continue to menstruate, cycles are notable for their variability in cycle interval and menses length due to reduced hormonal function, including shortened luteal phases (De Souza, 1998). Puberty may be delayed in girls who begin training before menarche (Frisch, 1981).

In 1970, Frisch and Revelle proposed the concept that an adolescent girl required a critical body weight to begin menstruating. This mass was initially postulated to be approximately 48 kg and was subsequently refined to a minimal body mass index (BMI) approaching the normal level of ≥19 (BMI = wt [kilograms]/height [meters]) (Table 1-7) (Frisch, 1974a, 1974b). Subsequent studies have suggested that, although there is a clear correlation between body fat and reproductive function (at both ends of the weight spectrum), overall energy balance better predicts the onset and maintenance of menstrual cycles (Billewicz, 1976; Johnston, 1975). For example, many elite athletes regain menstrual cyclicity following a decrease in exercise intensity prior to any change in weight (Abraham, 1982).

Table 16-7 Tests Commonly Used in the Evaluation of Amenorrhea

Primary laboratory tests	**Diagnosis**
β-hCG	Pregnancy
FSH	Hypogonadotropic versus hypergonadotropic hypogonadism[a]
Estradiol	Hypogonadotropic versus hypergonadotropic hypogonadism
Prolactin	Hyperprolactinemia
TSH	Thyroid disease (hypothyroidism)
Secondary laboratory tests	
Testosterone	PCOS and exclude ovarian tumor
DHEAS	Exclude adrenal tumor
17-OH-P	Late-onset CAH

2-hour glucose tolerance test	PCOS
Fasting lipid panel	PCOS
Autoimmune testing	Premature ovarian failure
Karyotype	Premature ovarian failure <35 years
Radiologic evaluation	
Sonography	PCOS or to determine presence of uterus
HSG or saline-infusion sonography	MÃ¼llerian anomaly or intrauterine synechiae
Magnetic resonance imaging	MÃ¼llerian anomaly or hypothalamic-pituitary disease

[a] Hypogonadotropic hypogonadism includes functional causes of hypothalamic amenorrhea (excessive exercise, eating disorders, and stress). Hypergonadotropic hypogonadism refers primarily to premature ovarian failure.

CAH = congenital adrenal hyperplasia; DHEAS = dehydroepiandrosterone sulfate; FSH = follicle-stimulating hormone; hCG = human chorionic gonadotropin; HSG = hysterosalpingography; 17-OH-P = 17-hydroxyprogesterone; PCOS = polycystic ovarian syndrome; TSH = thyroid-stimulating hormone.

Stress-Induced Amenorrhea

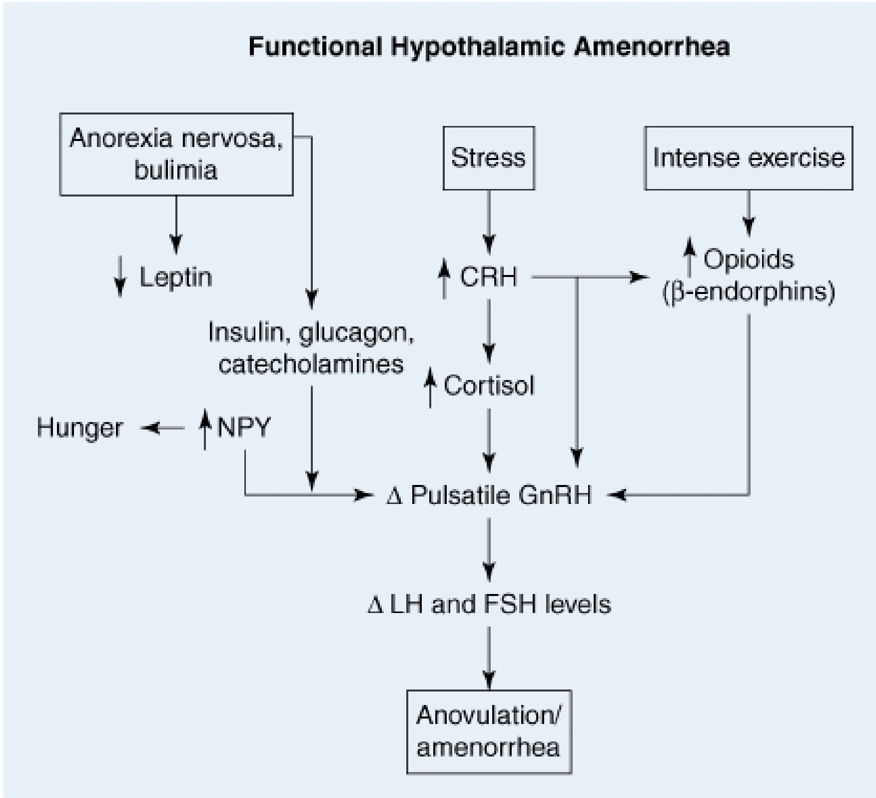
This may be associated with clearly traumatic life events, such as death of a family member or divorce. Nevertheless, much less severe life events and even positive events may be associated with stress. For example, stress-related amenorrhea is frequently associated with leaving for college, taking examinations, or wedding planning.

Eating disorders, exercise, and stress may alter menstrual function through overlapping mechanisms. This observation may be in part because these problems are often not found in isolation. For example, women with eating disorders frequently exercise excessively and are undoubtedly under stress as they attempt to control their eating patterns.

Pathophysiology of Functional Hypothalamic Amenorrhea

Figure 16-5 depicts a simplified model for the development of hypothalamic amenorrhea. It must be emphasized that each cause of functional hypothalamic amenorrhea may act via one or all of these pathways. Furthermore, in many cases, the factors known to impact reproductive function are likely acting indirectly on GnRH neurons via effects of various neuronal subtypes with synaptic connections to GnRH neurons.

FIGURE 16-5



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Diagram depicting a simplified model for the development of amenorrhea in women with eating disorders, high stress levels, or rigorous exercise. Δ = change in; CRH = corticotropin-releasing hormone; FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone; NPY = neuropeptide Y.

Exercise in particular has been associated with an increase in levels of endogenous opioids (β-endorphins), producing the so-called "runner's high". Opioids alter GnRH pulsatility as demonstrated by treatment of humans and animal models with anti-opiates, such as naloxone (see Chapter 15, Opioid Peptides and Gonadotropin-Releasing Hormone).

As part of the stress response, each of these conditions may lead to an increase in corticotropin-releasing hormone (CRH) release by the hypothalamus, which in turn results in cortisol secretion by the adrenal gland. Corticotropin-releasing hormone alters the pattern of pulsatile GnRH secretion, whereas cortisol may act directly or indirectly to disrupt GnRH neuronal function.

Eating disorders are thought to disrupt ovulatory function through a number of hormonal factors including insulin, glucagon, and leptin. First identified in 1994, leptin is a 167-amino acid protein encoded by the *ob* gene and produced in white adipose tissue (Zhang, 1994). Leptin receptors have been identified in the central nervous system as well as a wide range of peripheral tissues (Bjorbaek, 2004; Chen, 1996; Tartaglia, 1995, 1997).

Leptin provides an important link between energy balance and reproduction, albeit one of many mechanisms (Gonzalez, 2000; Schneider, 2004). Patients with anorexia nervosa have been found to have low circulating leptin levels (Mantzoros, 1997). Conversely, mutation of the human leptin gene results in morbid obesity, diabetes mellitus, and hypogonadism, which can be successfully reversed with recombinant human leptin (Janeckova, 2001; Licinio, 2004). Similarly, a mutation in the leptin-receptor gene has also been linked with hypogonadism and obesity (Farooqi, 2007).

This has led to the concept of leptin as a "satiety factor". It has been hypothesized that a decrease in leptin production due to

weight loss could secondarily stimulate neuropeptide Y, which is known to stimulate hunger and alter GnRH pulsatility. Leptin likely acts through a wide variety of additional neurotransmitters and neuropeptides including β-endorphins and α-melanocyte stimulating hormone (Tartaglia, 1995).

Pseudocysesis

Although rare, this diagnosis should be considered in any woman presenting with amenorrhea and pregnancy symptoms. Pseudocyesis exemplifies the ability of the mind to control physiologic processes. Approximately 550 cases have been reported in the medical literature in women ranging from 6 to 79 years. These patients fervently believe that they are pregnant and subsequently demonstrate a number of the signs and symptoms of pregnancy, including amenorrhea.

Endocrine evaluation in a limited number of patients has failed to demonstrate a consistent pattern of hormonal derangements. Alterations in LH pulse frequency in conjunction with elevated serum androgen levels may explain the development of amenorrhea. Elevated serum prolactin levels with resultant galactorrhea have been noted in a subset of patients. Growth hormone secretion appears to be blunted.

A common link in these patients is a history of severe grief, such as recent miscarriage or infant death. Psychiatric treatment is generally required to treat the associated depression, which is often exacerbated when the patient is informed that she is not pregnant (Bray, 1991; Starkman, 1985; Whelan, 1990).

Anatomic Destruction

Any process that destroys the hypothalamus can impair GnRH secretion and lead to the development of hypogonadotropic hypogonadism and amenorrhea. Due to the complex interaction of input to the GnRH neurons, these abnormalities do not need to directly impact the GnRH neurons, but may operate indirectly by altering activity of modulatory neurons.

Tumors most often associated with amenorrhea include craniopharyngiomas, germinomas, endodermal sinus tumors, eosinophilic granuloma (Hand-SchÃ¼ller-Christian syndrome), and gliomas, as well as metastatic lesions. The most common of these tumors, craniopharyngiomas, are located in the suprasellar region, and patients frequently present with headaches and visual changes.

Impaired GnRH secretion has also been reported with infections, such as tuberculosis, and with infiltrative diseases, such as sarcoidosis. Trauma or radiation to the hypothalamus can also result in hypothalamic dysfunction and subsequent amenorrhea.

ANTERIOR PITUITARY GLAND

The anterior pituitary gland consists of gonadotropes (producing LH and FSH), lactotropes (prolactin), thyrotropes (thyroid-stimulating hormone), corticotropes (adrenocorticotropin hormone), and somatotropes (growth hormone) (see Chap. 15, Anterior Pituitary Gland). Although various disorders may directly affect gonadotropes, many causes of pituitary-derived amenorrhea may also follow abnormalities in other pituitary cell types, which in turn, alter gonadotrope function.

Inherited Abnormalities of the Pituitary Gland

Rapid advances are being made in our understanding of the genetic mechanisms that regulate normal hypothalamic and pituitary development and function. Mutations resulting in the hypothalamic defect, Kallmann syndrome (hypogonadotropic hypogonadism with anosmia), have been described earlier. Additional genes known to affect hypothalamic development or function in the human will be mentioned here for completeness. Note that the clinical features observed in affected patients may vary widely depending on the severity of dysfunction that follows genetic mutation. Conversely, an identical mutation may have variable expression and clinical effects.

An increasing number of cohorts have been described with combined pituitary hormone deficiency and central facial and/or neurologic defects due to a failure of midline fusion. Known as septoptic dysplasia, many of these patients have a mutation in the *PROP1* gene (Cadman, 2006; Layman, 1999; Vesper, 2006). Mutations in genes that encode the LH or FSH β-subunits or the GnRH-receptor have also been identified as rare causes of hypogonadotropic hypogonadism. Hypothalamic and pituitary dysfunction with associated gonadal agenesis and adrenal hypoplasia has been well described in patients with mutations in the nuclear hormone receptors, steroidogenic factor-1 (SF-1; NR5A1) and DAX1 (NR0B1) (Beranova, 2001; Layman, 1997, 1998; Matthews, 1993; Weiss, 1992). Most recently, attention has focused on kisspeptin-1 and its receptor, G-protein-coupled receptor

54 (GPR54). Mutations in this receptor result in delayed puberty and hypogonadotropic hypogonadism, demonstrating that this ligand-receptor system is a critical stimulus of GnRH secretion (Pallais, 2006; Seminara, 2006).

Acquired Pituitary Dysfunction

Most pituitary dysfunction is acquired after menarche, and therefore, women present with normal pubertal development followed by secondary amenorrhea. Nevertheless, in rare cases, these disorders may develop prior to puberty, resulting in delayed pubertal development and primary amenorrhea (Howlett, 1989).

Pituitary adenomas are the most common cause of acquired pituitary dysfunction (see Chap. 15, Pituitary Adenomas). The most common adenomas secrete prolactin, however, altered secretion of any pituitary-derived hormone can result in amenorrhea.

As many as one tenth of amenorrheic women have increased levels of serum prolactin and more than half of women with both galactorrhea and amenorrhea have elevated prolactin levels (the "galactorrhea-amenorrhea syndrome"). Dopamine is the primary regulator of prolactin biosynthesis and secretion. Elevated prolactin levels are associated with a reflex increase in central dopamine production, which alters GnRH neuronal function.

Pituitary tumors also may indirectly alter gonadotrope function via a mass effect. This mass may compress neighboring gonadotropes or may damage the pituitary stalk, disrupting dopamine inhibition of prolactin secretion. Secondarily elevated prolactin levels presumably interfere with menstrual function through the same mechanisms described for primary prolactinomas above.

As in the hypothalamus, pituitary function may be disrupted by inflammation, infiltrative disease, or metastatic lesions. Although a rare condition, peripartum lymphocytic hypophysitis can be a dangerous cause of pituitary failure. Infiltrative diseases include sarcoidosis and hemochromatosis. In addition, loss of anterior pituitary function may be observed following surgical or radiation treatment of pituitary adenomas.

Sheehan syndrome refers to panhypopituitarism that develops after massive postpartum hemorrhage complicated by hypotension (Kelestimur, 2003). In its most severe form, patients develop shock and pituitary apoplexy. Loss of gonadotrope activity results in anovulation and subsequent amenorrhea. Damage to the other pituitary cell types may present as failure to lactate, loss of sexual and axillary hair, hypothyroidism, and adrenal insufficiency. The pituitary cell types are differentially sensitive to damage. Prolactin secretion deficiency is the most common, followed by loss of gonadotropin and growth hormone release, loss of ACTH, and least commonly, by decreases in thyroid-stimulating hormone (TSH) secretion (Veldhuis, 1980).

OTHER CAUSES OF HYPOGONADOTROPIC HYPOGONADISM

Hypogonadotropic amenorrhea may be observed in a wide variety of chronic diseases including end-stage kidney disease, liver disease, malignancies, acquired immunodeficiency syndrome, and malabsorption syndromes.

Eugonadotropic Amenorrhea

A number of disorders that produce amenorrhea are not associated with significantly abnormal gonadotropin levels. In these patients, chronic steroid secretion interferes with the normal feedback between the ovary and the hypothalamic-pituitary axis. The lack of cyclicity interferes with normal oocyte maturation, and menstruation fails to occur.

Due to relatively normal gonadotropin levels, these patients will secrete estrogen and therefore can be said to have *chronic anovulation with estrogen present.* This is in contrast to the patients with ovarian failure or hypothalamic-pituitary failure in which estrogen is low. This distinction may be useful during evaluation and treatment.

POLYCYSTIC OVARIAN SYNDROME

This syndrome is by far the most common cause of chronic anovulation with estrogen present (see Chap. 17). Patients with polycystic ovarian syndrome (PCOS) may have a wide variety of menstrual presentations, ranging from occasional ovulatory cycles to menometrorrhagia secondary to unopposed estrogen stimulation of the endometrium to complete amenorrhea. Amenorrhea in PCOS patients may be attributable in part to the atrophic effects of androgens on endometrial proliferation.

Polycystic ovarian syndrome can be appropriately characterized as an inherited form of eugonadotropic amenorrhea. Although a

specific gene defect has not been identified, there is an increased incidence of PCOS in the mothers and sisters of affected individuals. An elevated ratio of LH:FSH levels (greater than twofold) has been noted in most patients, however, the LH level remains in the normal or high-normal range.

ADULT-ONSET CONGENITAL ADRENAL HYPERPLASIA

This condition closely mimics the presentation of PCOS, with hyperandrogenism and irregular menstrual cycles. Most commonly, late-onset congenital adrenal hyperplasia (CAH), also termed adult-onset CAH, is due to a mutation in the *CYP21* gene, which encodes the 21-hydroxylase enzyme. With a mild mutation, patients are asymptomatic until adrenarche and its associated requirement for increased adrenal steroidogenesis. Patients with CAH are unable to convert an adequate percentage of progesterone to cortisol and aldosterone, thus increasing the production of androgens (see Fig. 15-13). As in PCOS, elevated androgen levels blunt oocyte maturation and thereby result in anovulation and amenorrhea. Congenital adrenal hyperplasia is additionally discussed in Chapter 15, Congenital Adrenal Hyperplasia and 18, Pathophysiology.

OVARIAN TUMOR

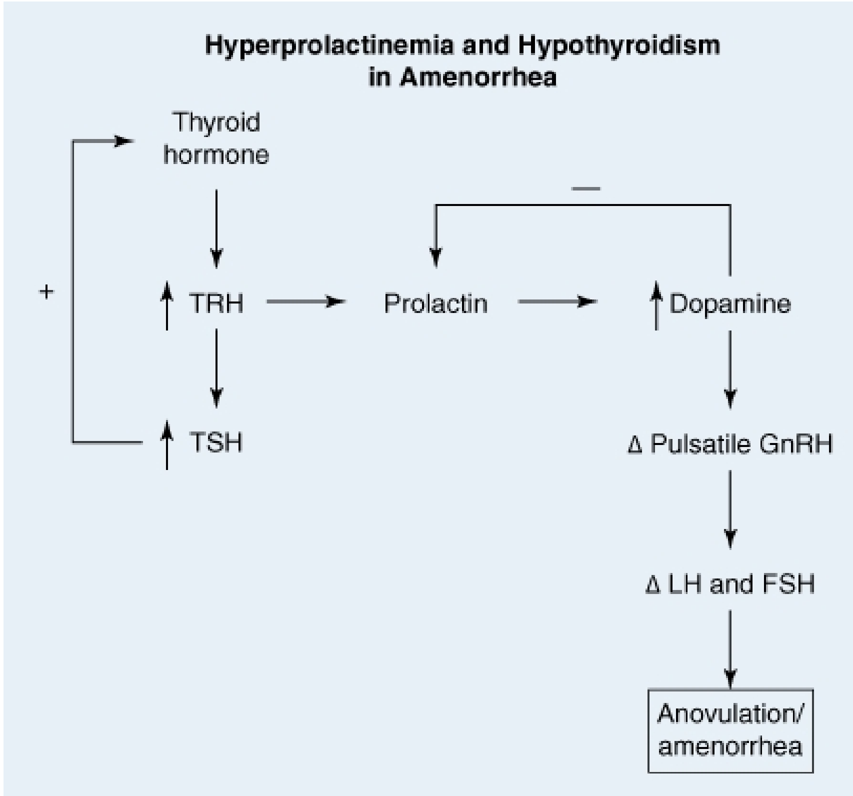
Although uncommon, chronic anovulation with estrogen present can also be observed with ovarian tumors producing either estrogens or androgens. Examples of these neoplasms include granulosa cell tumors, and thecal cell tumors, which are sex steroid-stromal tumors (see Chap. 36, Ovarian Sex Cordâ€“Stromal Tumors).

HYPERPROLACTINEMIA AND HYPOTHYROIDISM

As discussed above, hyperprolactinemia can be categorized as a cause of pituitary hypogonadotropic hypogonadism. Of note, however, many of these patients may have relatively normal gonadotropin levels, although as a group their estrogen levels will be mildly depressed. Thyroid disease is also a relatively common cause of oligomenorrhea associated with gonadotropins in the normal range. Classically, hypothyroidism is stated to cause amenorrhea, whereas hyperthyroidism is implicated in menorrhagia.

A mechanism by which hyperprolactinemia and hypothyroidism may lead to amenorrhea is outlined in Figure 16-6. In this model, a primary decrease in circulating thyroid hormone levels, for example due to Hashimoto thyroiditis, leads to a compensatory increase in hypothalamic thyrotropin-releasing hormone (TRH). As part of the thyroid axis, TRH increases TSH by the pituitary gland thyrotropes. In addition, TRH also binds to the pituitary lactotropes, increasing prolactin secretion.

FIGURE 16-6



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Diagram depicting a simplified model for the development of amenorrhea in women with hyperprolactinemia or hypothyroidism. Δ = change in; FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone; TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone.

An increase in circulating prolactin results in a compensatory increase in central dopamine, the primary inhibitor of prolactin secretion. The increase in central dopamine levels alters GnRH secretion, thereby disrupting normal cyclic gonadotropin secretion and preventing ovulation. Note that this increase in prolactin may be primary, for example from a prolactinoma, or may be secondary due to an elevation in TRH. In secondary hyperprolactinemia, prolactin levels are generally lower and less than 100 ng/mL.

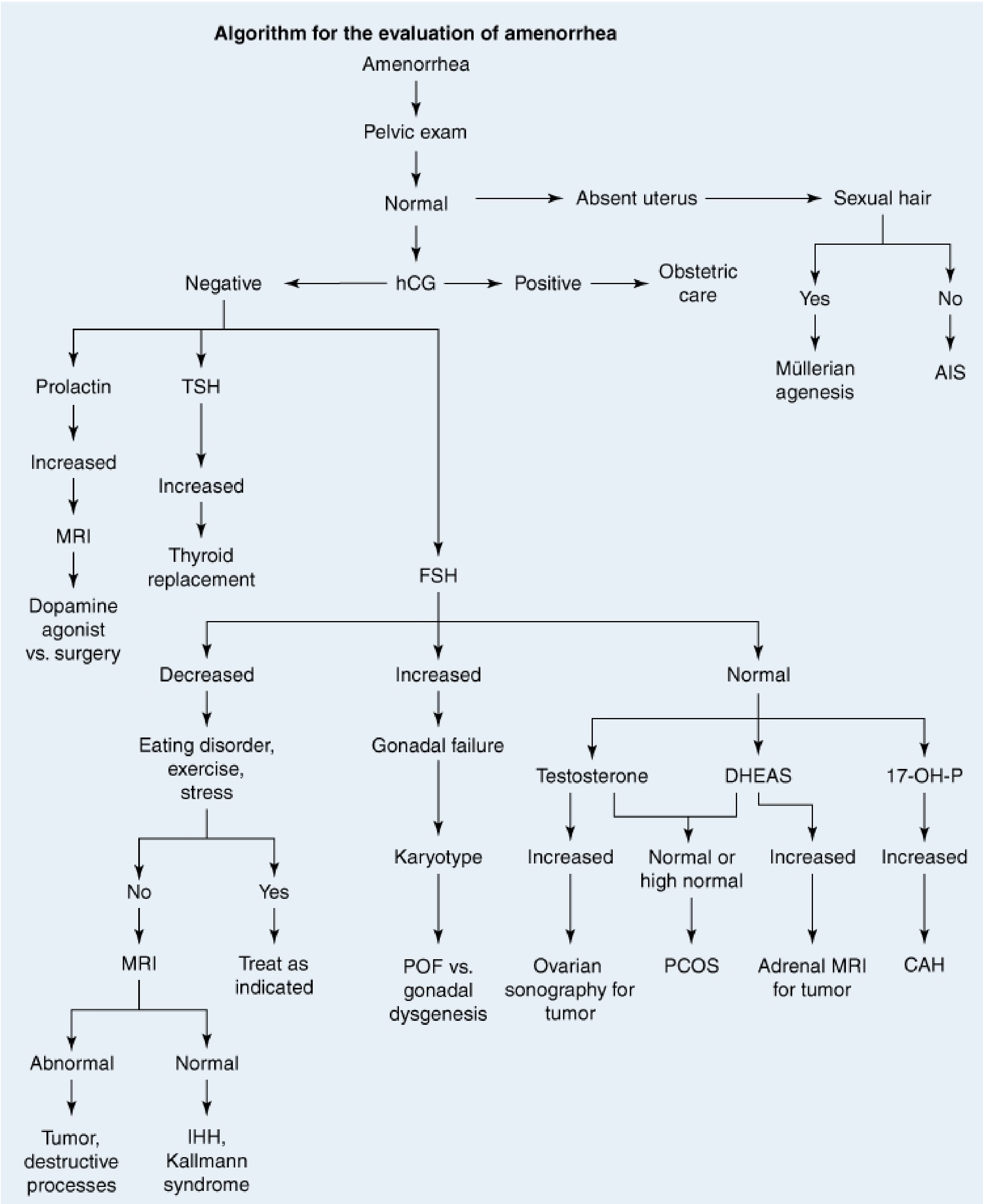
There are undoubtedly other mechanisms by which thyroid disease and elevated prolactin levels disturb menstrual function, but these are poorly understood at present. For example, thyroid receptors are found in most cell types. Moreover, thyroid hormone increases sex-hormone binding globulin levels, altering the levels of unbound, and thereby active, ovarian steroids. In addition, prolactin receptors have been identified in the ovary and in the endometrium.

EVALUATION

History

An algorithm for approaching the patient with amenorrhea is presented in Figure 16-7. The evaluation of menstrual abnormalities should start with questions regarding pubertal development. Did the patient experience normal puberty in terms of onset and progression (see Chap. 14, Pubertal Changes)? Did she ever achieve regular menstrual cyclicity? The cycle interval, duration, and amount of menstrual flow should be characterized. It is important to determine when a change in this pattern was noted and whether the change was sudden or gradual. Did the development of amenorrhea correlate with pelvic infection, surgery, radiation, chemotherapy, or other illness?

FIGURE 16-7



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Diagnostic algorithm to evaluate amenorrhea. AIS = androgen insensitivity syndrome; CAH = congenital adrenal hyperplasia; DHEA-S = dehydroepiandrosterone sulfate; FSH = follicle-stimulating hormone; hCG = human chorionic gonadotropin; IHH = idiopathic hypogonadotropic hypogonadism; MRI = magnetic resonance imaging; 17-OH-P = 17-hydroxyprogesterone; PCOS = polycystic ovarian syndrome; POF = premature ovarian failure; TSH = thyroid-stimulating hormone.

In addition, a thorough medical history should be obtained. A surgical history should focus on prior pelvic surgery, particularly intrauterine surgery, including dilatation and curettage. Complications associated with uterine surgery, particularly infection, should be sought.

A focused review of symptoms can also be helpful in defining the etiology of amenorrhea. For example, new-onset headaches or visual changes may suggest a tumor of the central nervous system or pituitary gland. Spontaneous bilateral breast discharge is consistent with a diagnosis of hyperprolactinemia. The presence of thyroid disease may be associated with heat or cold intolerance, weight changes, and sleep abnormalities. Hot flashes and vaginal dryness suggest hypergonadotropic hypogonadism or POF. Hirsutism and acne are frequently seen with PCOS, or with late-onset CAH. Cyclic pelvic pain would suggest a reproductive tract outlet obstruction.

Important questions regarding family history include premature cessation of menses or a history of autoimmune disease, including thyroid disease, which would suggest an increased risk for POF. A family history of irregular menses, infertility, or signs of excess androgen production may be noted in a patient with PCOS. Sudden neonatal death may have occurred in family members carrying mutations in the *CYP21* gene responsible for classic CAH.

The social history should investigate exposure to environmental toxins, including cigarettes. Any medications, especially those that increase prolactin levels such as antipsychotics should be noted (see Table 12-4).

Physical Examination

A thorough physical examination will frequently provide a diagnosis, although testing is still indicated. General appearance can be helpful in the evaluation of amenorrhea. A low body mass index, perhaps in conjunction with loss of tooth enamel due to recurrent vomiting, is highly suggestive for an eating disorder. Signs of Turner syndrome should be evaluated, including the presence of short stature and other stigmata such as webbed neck or shield-shaped chest. Midline facial defects, such as cleft palate, are consistent with a developmental defect of the anterior pituitary gland. Hypertension in a prepubertal girl would be consistent with mutation in the *CYP17* gene and CAH.

Visual field changes, particularly bitemporal hemianopsia, or other visual defects may be indicative of a tumor in the pituitary gland or central nervous system.

Skin should be inspected for acanthosis nigricans, hirsutism, or acne, which may indicate PCOS or other causes of hyperandrogenism (see Figs. 17-7). The presence of supraclavicular fat and abdominal striae with hypertension may be noted in those with Cushing syndrome. Hypothyroidism may present with an abnormally enlarged thyroid gland, delayed reflexes, and bradycardia. On breast examination, bilateral galactorrhea implies the presence of hyperprolactinemia. A more complete discussion of the evaluation and treatment of galactorrhea can be found in Chapter 12, Nipple Discharge.

Examination of the genitalia should start by noting hair pattern. Sparse or absent female pubic hair may be due to either lack of adrenarche or androgen insensitivity syndrome. Conversely, elevated androgen levels will result in a male pattern of genital hair growth. In contrast to the triangular pattern of hair in females, male abdominal wall hair extends to the umbilicus, forming a triangle, or male escutcheon (see Fig. 17-3). Markedly elevated levels of androgens will produce signs of virilization, most noticeably clitoromegaly. These women may also note voice deepening and male pattern balding.

Evidence of estrogen production includes a pink moist vagina and cervical mucus. A vaginal smear will demonstrate a majority of superficial epithelial cells (see Fig. 21-12).

Determination of mÃ¼llerian anomalies by physical examination is described in Chapter 18, MÃ¼llerian Anomalies. A rectal examination may help identify a uterus above an obstruction at the level of the introitus or in the vagina. The presence of hematocolpos suggests normal ovarian and endometrial function.

Laboratory and Radiologic Testing

Although the differential diagnosis of amenorrhea is extensive, evaluation of most women is relatively straightforward. As for all disorders, testing will be modified by patient history and physical examination.

EXCLUSION OF PREGNANCY

All reproductive-aged women with amenorrhea should be assumed pregnant until proven otherwise. Therefore, it is always prudent to measure a urinary or serum β-hCG level.

PROGESTERONE WITHDRAWAL

Classically, patients are given exogenous progesterone and monitored for a progesterone withdrawal bleed, which follows a few days after completion of progesterone (progesterone challenge test). If bleeding ensues, then a woman is assumed to produce estrogen and to have an intact endometrium and patent outflow tract. If bleeding does not follow, then a patient is given estrogen followed by progesterone treatment. If a woman again fails to bleed, then an anatomic abnormality is diagnosed.

However, a number of factors can lead to an incorrect test interpretation. First, estrogen levels may fluctuate in both hypothalamic amenorrhea and in the early stages of ovarian failure. As a result, patients with these disorders may have at least some bleeding after progesterone withdrawal. Furthermore, women with high androgen levels, such as occurs with PCOS and CAH, may have an atrophic endometrium and fail to bleed. Specifically, up to 20 percent of women in whom estrogen is present will fail to bleed following progesterone withdrawal (Rarick, 1990). Conversely, menses may be observed in up to 40 percent of women with hypothalamic amenorrhea due to stress, weight loss, or exercise, and in up to 50 percent of women with ovarian failure after progesterone administration (Nakamura, 1996; Rebar, 1990).

SERUM HORMONE LEVELS

As suggested by the American Society for Reproductive Medicine (2006), it may be more reasonable to begin with hormonal evaluation in any woman found to have a normal pelvic examination (Table 16-7).

Follicle-Stimulating Hormone

A normal FSH level suggests an anatomic defect or eugonadotropic hypogonadism, such as PCOS. In contrast, an elevated FSH level is consistent with ovarian failure, and a low level suggests hypothalamic-pituitary dysfunction.

Patients with PCOS, hyperprolactinemia, or thyroid disease would be expected to have normal FSH levels. Although many patients with PCOS have elevated LH:FSH level ratios (>2), testing for this relationship is unnecessary, as a normal ratio does not exclude this diagnosis.

An elevated FSH level strongly suggests the presence of hypergonadotropic hypogonadism (premature ovarian failure). This diagnosis requires two FSH levels >40 mIU/mL obtained at least 1 month apart. Many clinicians will simultaneously obtain an estradiol level to further confirm the diagnosis, although this has not been shown to substantially increase diagnostic accuracy. At least two elevated values are required because the course of POF may fluctuate over time. It is likely that this fluctuation explains the occasional pregnancy that has been reported in these patients. Patients should keep a menstrual calendar while testing is completed, as bleeding 2 weeks following an elevated serum FSH level may simply indicate that the sample was obtained during a gonadotropin surge.

If an FSH value is low, it may be helpful to repeat this measurement with the addition of an LH level to confirm hypogonadotropic hypogonadism. Additional testing may include a GnRH stimulation test. Although a number of different protocols have been employed, one common approach has been intravenous injection of 100 μg of GnRH as a bolus followed by measurement of LH and FSH at 0, 15, 30, 45, and 60 minutes. Although both LH and FSH levels will be blunted, FSH levels will be high relative to LH ratios in patients with hypogonadotropic hypogonadism or delayed puberty (Job, 1977; Yen, 1973). Although informative, in practice this test is often unable to be performed due to a lack of consistently available clinical-grade GnRH.

Prolactin and Thyroid-Stimulating Hormone

These hormone levels should be tested in most patients with amenorrhea, as prolactin-secreting adenomas and thyroid disease are

relatively common and require specific treatment. Furthermore, hypothyroidism may secondarily lead to elevated prolactin levels as shown in Figure 16-6. Because of this close relationship between thyroid disease and prolactin levels, both hormones should be measured simultaneously. Treatment for hypothyroidism will also normalize prolactin levels. Regrettably, it is not uncommon for patients to be imaged and subsequently treated for hyperprolactinemia with delay in diagnosis of their primary hypothyroidism (Poretsky, 1986).

Testosterone

Serum levels of this hormone should be measured in any woman with suspected PCOS or with clinical signs of androgen excess. Hormonal evaluation should include evaluation of serum total testosterone levels. Measurement of free testosterone levels is generally unwarranted, as these assays are more expensive and more variable. Mild elevations in testosterone levels are consistent with the diagnosis of PCOS. However, values exceeding 200 ng/dL are consistent with the presence of an ovarian tumor and should be evaluated with pelvic sonography.

Dehydroepiandrosterone Sulfate

Secretion of this hormone is essentially limited to the adrenal gland. High normal levels or even very mild elevations are consistent with PCOS. In contrast, adrenal adenomas may produce circulating DHEAS levels above 700 μg/dL and warrant investigation with magnetic resonance (MR) imaging or computed tomography (CT) of the adrenals. Measurement of 17-hydroxyprogesterone (17-OH-P) aims to identify patients with late-onset CAH. However, confirmation of this diagnosis can be difficult due to the overlap in values among normal patients and heterozygote and homozygote carriers of mutations in the gene that encodes 21-hydroxylase (*CYP21A2*). Therefore, stimulation with ACTH, often colloquially termed the *cort stim test,* may be required (see Chap. 17, 17-Hydroxyprogesterone).

OTHER SERUM TESTING

If there is any suggestion of an eating disorder, an immediate assessment of serum electrolytes is indicated, as imbalances can be life-threatening. An electrocardiogram should also be considered in those patients perceived to have more severe disease. A reverse triiodothyronine (T_3) level is often elevated in patients with functional hypothalamic amenorrhea.

Women with PCOS should be screened for insulin resistance and lipid abnormalities, as these are commonly found in affected patients and increase risks for development of diabetes and cardiovascular disease (see Chap. 17, Impaired Glucose Tolerance and Type 2 Diabetes Mellitus). Although no consensus exists, it is probably prudent to repeat these tests every few years in these women.

RADIOLOGIC EVALUATION

Any patient with hypogonadotropic hypogonadism should be assumed to have an anatomic abnormality until proven otherwise by imaging of the brain and pituitary gland with MR imaging or a CT scan. Thus, functional hypothalamic amenorrhea due to stress, exercise, or eating disorder is a diagnosis of exclusion. Imaging is highly sensitive for identification of destructive disorders such as tumors or infiltrative diseases of the hypothalamus or pituitary. Patients with Kallmann syndrome frequently demonstrate defects in the development of the olfactory bulbs and sulci of the rhinencephalon (Klingmuller, 1987).

CHROMOSOMAL ANALYSIS

Patients with gonadal dysgenesis, such as Turner syndrome, should be considered for karyotype testing. Classic teaching suggests that this test is unnecessary after age 30. However, consideration should be given to testing patients up to age 35 years, as a rare patient with mosaicism may sustain cyclic menses longer than expected. As previously indicated, a Y-cell line requires bilateral oophorectomy because of the increased risk for ovarian tumors. Due to the close association between stature and abnormalities in the X-chromosome, many specialists advise karyotyping all women with POF who are shorter than 60 inches. Chromosomal studies should also be considered in any woman with a familial history of POF.

SPECIFIC DISORDERS

Premature Ovarian Failure

Many patients with POF will not have a clear etiology for their disorder. Presumption of an autoimmune cause is probably wise,

based on the potential long-term consequences of these disorders. Testing varies widely among experts, but those that may be associated with POF are listed in Table 16-8.

Table 16-8 Evaluation of Premature Ovarian Failure Due to Presumptive Autoimmune Disease

Test(s)	Target Organ
Free T4, TSH, ATA, AMA	Thyroid
Calcium, phosphorus, albumin	Parathyroid
ACTH	Adrenal
Fasting glucose	Islet cells
Complete blood count	Red blood cells (hemolytic anemia or pernicious anemia)
Platelets	Idiopathic thrombocytopenia
ANA, RF, ESR	General autoimmune disease screen

ACTH = adrenocorticotropin hormone; AMA = anti-microsomal antibody; ANA = anti-nuclear antibody; ATA =anti-thyroid antibody; ESR = erythrocyte sedimentation rate; RF = rheumatoid factor; TSH = thyroid-stimulating hormone; T4 = thyroxine.

Anatomic Disorders

These can be evaluated with a number of modalities depending on the suspected etiology. Sonographic examination is frequently useful as a first screen for those with a grossly normal uterus. Hysterosalpingography (HSG) and saline-infusion sonography (SIS) are excellent for the detection of intrauterine synechiae or developmental anomalies (see Chaps. 2, Infertility and 19, Uterine Pathology). Magnetic resonance (MR) imaging is frequently used for delineation of anatomic structures, such as mÃ¼llerian anomalies and others (see Figs. Chaps. 2, Congenital Anomalies and 18, Diagnosis and Treatment).

MÃ¼llerian dysgenesis may be associated with a variety of malformations in other organ systems. With complete mÃ¼llerian agenesis, approximately one third of patients will have urinary tract abnormalities including an ectopic kidney, unilateral renal agenesis, horseshoe kidney, or abnormal collecting ducts. Skeletal anomalies, generally of the spine, may be present in up to 12 percent of these patients (Fore, 1975; Griffin, 1976). A renal sonographic examination and lower spine radiographic evaluation will detect these associated anomalies. The incidence of these related anomalies differs between the types of mÃ¼llerian dysgenesis. They are probably most common with complete agenesis or duplication anomalies, such as bicornuate uterus or uterine didelphys, and less common with disorders of resorption, such as a uterine septum (Fedele, 1990; Letterie, 1988; Reinhold, 1997). For this reason, most experts feel that additional anatomic evaluation is not required in those with a uterine septum and no other uterine anomalies.

Magnetic resonance (MR) imaging is also helpful to detect endometrial tissue in a uterus or uterine horns. A noncommunicating uterine horn with a clear endometrial stripe should be removed in most instances, as it increases the risk of endometriosis and may ultimately cause pain due to distension with menstrual blood. Furthermore, if a pregnancy occurs in this horn, it will almost invariably lead to uterine rupture.

TREATMENT

The treatment of amenorrhea depends on the etiology as well as the aims of the patient, such as a desire to treat hirsutism or to become pregnant.

Anatomic abnormalities will require surgical correction, if possible. Hypothyroidism should be treated with thyroid replacement, and patients with hyperprolactinemia should receive a dopamine agonist, such as bromocriptine or cabergoline (see Chap. 15, Treatment of Pituitary Adenomas). Macroadenomas may require surgery if secondary deficits, such as visual changes, are observed

(see Chap. 15, Pregnancy and Pituitary Adenomas).

Estrogen Replacement

This therapy should be instituted in essentially every patient with hypogonadism to avoid osteoporosis (see Chap. 21, Bone Metabolism and Structural Changes). As in postmenopausal women, bone loss is accelerated in the first few years following estrogen deprivation, and therefore treatment should be instituted quickly. Women with a uterus also require continuous or intermittent progesterone administration to protect against endometrial hyperplasia or cancer (see Chap. 22, Summary of Current Use Indications).

There is no consensus, however, on an optimal regimen in these patients. A listing of available estrogens and progestins used for hormone replacement therapy is found in Table 22-2. Some experts recommend that women in their twenties should receive higher doses of estrogen than is routinely given to postmenopausal women, as this is a time of ongoing bone deposition. Frequently, it is easiest to prescribe combination oral contraceptive pills. Younger women may prefer this treatment, as their friends may also use these pills, and in their minds hormone replacement therapy may be associated with aging. Additionally, there is also no consensus on the duration of treatment in this patient population. For most patients, continuation until approximately age 50, the usual age of menopause, seems reasonable.

Patients who have eating disorders or who exercise excessively will require behavior modification. In a patient with an eating disorder, psychiatric intervention is imperative due to the significant morbidity and mortality associated with this diagnosis (American Psychiatric Association, 2000). Elite athletes may choose not to alter their exercise regimens and will therefore require estrogen treatment.

Polycystic Ovarian Syndrome

Treatment of affected women may include cyclic progesterone treatment or oral contraceptives or other forms of estrogen-progesterone treatment (see Chap. 17, Combination Oral Contraceptive Pills). Insulin-sensitizing agents such as metformin (Glucophage, Bristol-Myers Squibb, New York, NY) may be indicated in those with insulin resistance. Hyperandrogenism due to PCOS may be treated with oral contraceptives and/or spironolactone.

Women with late-onset CAH may be treated with low-dose corticosteroids to partially block ACTH stimulation of adrenal function and thereby decrease overproduction of adrenal androgens.

Infertility

Treatments may require modification if a woman desires conception. Adequate treatment of hyperprolactinemia and thyroid disease will result in ovulation and in normal fertility for most women. Anatomic abnormalities will often require attempts at surgical correction. However, if adequate correction is impossible, pregnancy will require use of a surrogate to carry a gestation. Premature ovarian failure cannot be corrected, and these patients will require in vitro fertilization using a donor oocyte to conceive. In contrast, patients with hypogonadotropic hypogonadism typically require treatment with pulsatile GnRH or gonadotropins. As pulsatile GnRH is more complex to administer, most patients receive gonadotropin therapy from an infertility specialist. Patients with PCOS will frequently ovulate following clomiphene citrate treatment. Clomiphene citrate is believed to act by transient inhibition of estrogen feedback at the hypothalamus and pituitary gland. Therefore, this treatment will not be effective in patients with hypogonadotropic hypogonadism, as they lack estrogen synthesis.

Patient Education

Finally, as in all medical conditions, it is critical that patients be adequately counseled about their diagnosis, the long-term implications of this diagnosis, and the treatment options. Even if not raised by the patient, the potential for future childbearing should be discussed. Many women are under the mistaken impression that it is dangerous not to have a menstrual period, and should be reassured that this is, in and of itself, not a concern. On the other hand, all women with an intact endometrium should understand the risks of unopposed estrogen action, whether the estrogen is exogenous such as through hormone therapy, or endogenous such as in PCOS. Hypoestrogenic women should be counseled about the importance of estrogen replacement to protect against bone loss. As discussed in Chapter 22, Summary of Current Use Indications, estrogen may have additional benefits, which

should also be discussed with these women.

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POLYCYSTIC OVARIAN SYNDROME AND HYPERANDROGENISM: INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a common endocrinopathy typified by oligo-ovulation or anovulation, signs of androgen excess, and multiple small ovarian cysts. These signs and symptoms may vary widely between women as well as within individuals over time. As a result, women with PCOS may present to various medical specialists, including gynecologists, internal medicine specialists, endocrinologists, or dermatologists. Thus, a familiarity with PCOS is essential for physicians in each of these specialties.

INCIDENCE

Polycystic ovarian syndrome is the most common endocrine disorder of reproductive-aged women and affects approximately 4 to 12 percent (AsunciÃ³n, 2000; Diamanti-Kandarakis, 1999; Farah, 1999: Knochenhauer, 1998). Although symptoms of androgen excess may vary between ethnicity, PCOS appears to equally affect all races and nationalities.

DEFINITIONS

Polycystic Ovarian Syndrome

In 2003 in Rotterdam, Netherlands, a consensus meeting between the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine (ESHRE/ASRM) (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004) redefined PCOS (Table 17-1). Affected individuals must have two out of the following three criteria: (1) oligo- and/or anovulation, (2) hyperandrogenism (clinical and/or biochemical), and (3) polycystic ovaries on sonographic examination. However, because other etiologies, such as congenital adrenal hyperplasia, androgen-secreting tumors, and hyperprolactinemia, may also lead to oligo-ovulation and/or androgen excess, these must be excluded. Thus, PCOS is at present a diagnosis of exclusion.

Table 17-1 Definition of Polycystic Ovarian Syndrome
ESHRE/ASRM (Rotterdam) 2003 To include two out of three of the following: 1. Oligo or anovulation 2. Clinical and/or biochemical signs of hyperandrogenism 3. Polycystic ovaries (with the exclusion of related disorders)
NIH (1990) To include both of the following: 1. Oligo-ovulation 2. Hyperandrogenism and/or hyperandrogenemia (with the exclusion of related disorders)

ASRM = American Society of Reproductive Medicine; ESHRE = European Society of Human Reproduction and Embryology; NIH = National Institutes of Health.

From The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004, and Zawadzki, 1990, with permission.

The Rotterdam criteria constitute a broader spectrum than that formerly put forward by the National Institutes of Health (NIH) Conference in 1990 (Zawadzki, 1990). The latter defined PCOS by ovulatory dysfunction plus clinical hyperandrogenism and/or hyperandrogenemia without regard to ovarian sonographic appearance. Controversy exists as to which definition is more appropriate, and many investigators still use the NIH 1990 criteria as a basis to define PCOS in their population studies (Chang, 2005).

Ovarian Hyperthecosis and HAIRAN Syndrome

Often considered a more severe form of PCOS, *ovarian hyperthecosis* is a rare condition characterized by nests of luteinized theca cells distributed throughout the ovarian stroma. Affected women exhibit severe hyperandrogenism, and may occasionally display frank virilization signs such as clitoromegaly, temporal balding, and deepening of the voice (Culiner, 1949). In addition, there is typically a much greater degree of insulin resistance and acanthosis nigricans (Nagamani, 1986).

The hyperandrogenic-insulin resistant-acanthosis nigricans (HAIRAN) syndrome is uncommon and consists of marked hyperandrogenism, severe insulin resistance, and acanthosis nigricans (Barbieri, 1994). The etiology of this disorder is unclear, and HAIRAN syndrome may represent either a variant of PCOS or a distinct genetic syndrome.

ETIOLOGY

The underlying cause of PCOS is unknown. However, a genetic basis that is both multifactorial and polygenic is suspected, as there is a well-documented aggregation of the syndrome within families (Franks, 1997). Specifically, an increased prevalence has been noted between affected individuals and their sisters (32 to 66 percent) and mothers (24 to 52 percent) (Govind, 1999; Kahsar-Miller, 2001; Yildiz, 2003). Some have suggested an autosomal dominant inheritance with expression in both females and males. For example, first-degree male relatives of women with PCOS have been shown to have significantly higher circulating dehydroepiandrosterone sulfate (DHEAS) levels than control males (Legro, 2002).

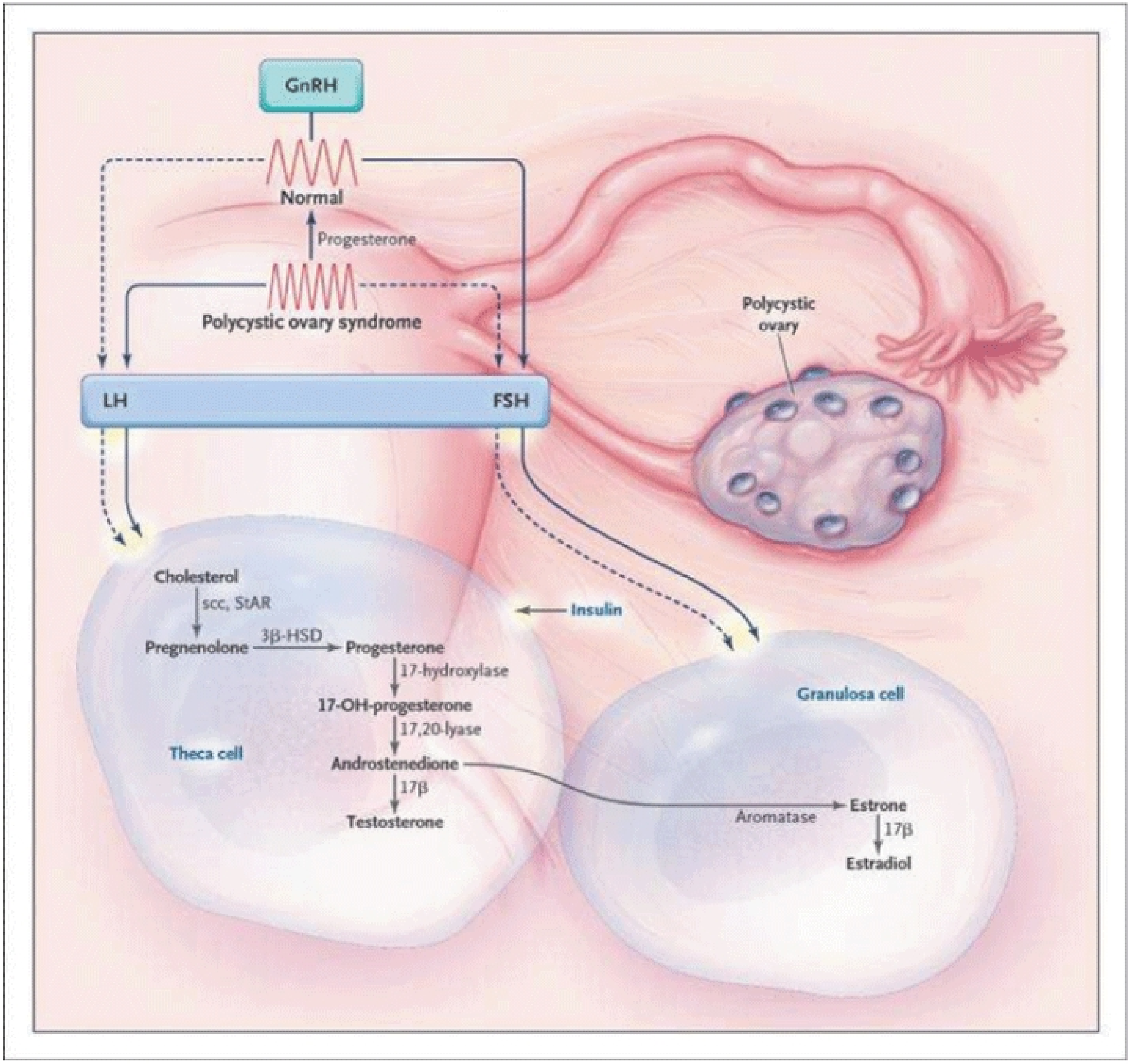
Identification of candidate genes linked to PCOS has been a major research focus, given the large potential benefit for both diagnosis and management of this disorder. Clinical and in vitro studies of human ovarian theca cells have suggested dysregulation of the *CYP11a* gene in patients with PCOS. This gene encodes the cholesterol side-chain cleavage enzyme, the enzyme that performs the rate-limiting step in steroid biosynthesis(see Fig. 15-13). Evidence also suggests upregulation of other enzymes in the androgen biosynthetic pathway (Franks, 2006). In addition, the insulin receptor gene on chromosome 19p13.2 may be involved (Urbanek, 2005). Further investigation, however, is needed to determine the roles of these gene products in the pathogenesis of PCOS.

PATHOPHYSIOLOGY

Gonadotropins

Anovulation in women with PCOS is characterized by inappropriate gonadotropin secretion (Figs. 17-1 and 17-2). Alterations in gonadotropin-releasing hormone (GnRH) pulsatility lead to preferential production of luteinizing hormone (LH) compared with follicle-stimulating hormone (FSH) (Hayes, 1998; Waldstreicher, 1988). It is currently unknown whether hypothalamic dysfunction is a primary cause of PCOS or is secondary to abnormal steroid feedback. In either case, serum LH levels rise, and increased levels are observed clinically in approximately 50 percent of affected women (Balen, 2002, van Santbrink, 1997). Similarly, luteinizing hormone:follicle-stimulating hormone (LH:FSH) ratios are elevated and rise above 2 in approximately 60 percent of patients (Rebar, 1976).

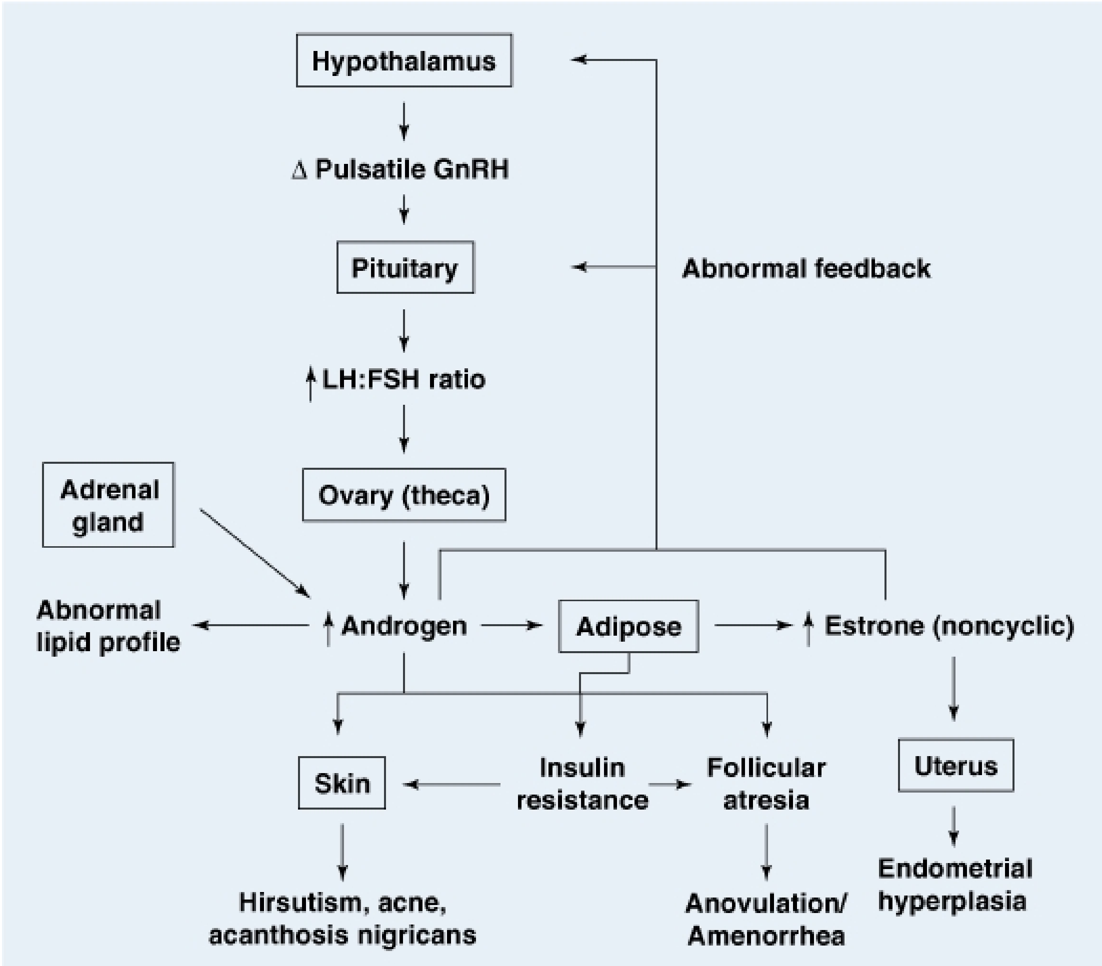
FIGURE 17-1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Suggested pathophysiologic mechanism for increased androgen and estrogen production associated with polycystic ovarian syndrome. FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; 3β-HSD = 3β-hydroxysteroid dehydrogenase; LH = luteinizing hormone; scc = side-chain cleavage enzyme; StAR = steroidogenic acute regulatory protein. *(From Ehrmann, 2005, with permission.)*

FIGURE 17-2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Model for the initiation and maintenance of polycystic ovarian syndrome (PCOS). Alterations in pulsatile gonadotropin-releasing hormone (GnRH) release may lead to a relative increase in luteinizing hormone (LH) versus follicle-stimulating hormone (FSH) biosynthesis and secretion. LH stimulates ovarian androgen production, while the relative paucity of FSH prevents adequate stimulation of aromatase activity within the granulosa cells, thereby decreasing androgen conversion to the potent estrogen estradiol.

Increased intrafollicular androgen levels result in follicular atresia. Increased circulating androgen levels contribute to abnormalities in patient lipid profiles and the development of hirsutism and acne. Increased circulating androgens can also be derived from the adrenal gland.

Elevated serum androgens (primarily androstenedione) are converted in the periphery to estrogens (primarily estrone). As conversion occurs primarily in the stromal cells of adipose tissue, estrogen production will be augmented in obese PCOS patients. This conversion results in chronic feedback at the hypothalamus and pituitary gland, in contrast to the normal fluctuations in feedback observed in the presence of a growing follicle and rapidly changing levels of estradiol. Unopposed estrogen stimulation of the endometrium may lead to endometrial hyperplasia.

Insulin resistance due to genetic abnormalities and/or increased adipose tissue contributes to follicular atresia in the ovaries as well as the development of acanthosis nigricans in the skin.

Lack of follicular development results in anovulation and subsequent oligo-amenorrhea.

Note that this syndrome may develop from primary dysfunction of any one of a number of organ systems. For example, elevated ovarian androgen production may be due to either an intrinsic abnormality in enzymatic function and/or abnormal hypothalamic-pituitary stimulation with LH and FSH.

The common denominator is development of a self-perpetuating noncyclic hormonal pattern.

Insulin Resistance

Women with PCOS also display greater degrees of insulin resistance and compensatory hyperinsulinemia than nonaffected women. Insulin resistance is defined as a reduced glucose response to a given amount of insulin. The mechanism of this decreased insulin sensitivity appears to be due to a postbinding abnormality in insulin receptor-mediated signal transduction (Dunaif, 1997). Both lean and obese women with PCOS are found to be more insulin resistant than nonaffected weight-matched controls (Dunaif 1989, 1992).

Insulin resistance has been associated with an increase in several disorders including type 2 diabetes mellitus, hypertension, dyslipidemia, and cardiovascular disease. Therefore, PCOS is not simply a disorder of short-term consequences such as irregular periods and hirsutism, but also one of long-term heath consequences (Table 17-2).

Table 17-2 Consequences of Polycystic Ovarian Syndrome
Short-term consequences 1. Irregular menses 2. Hirsutism/acne/androgenic alopecia 3. Infertility 4. Obesity 5. Metabolic disturbances 6. Abnormal lipid levels/glucose intolerance
Long-term consequences 1. Diabetes mellitus 2. Cardiovascular disease 3. Endometrial cancer

Androgens

Both insulin and LH stimulate ovarian theca cell androgen production (Dunaif, 1992). As a result, affected ovaries secrete elevated levels of testosterone and androstenedione. Specifically, elevated free testosterone levels are noted in 70 to 80 percent of women with PCOS, and 25 to 65 percent exhibit elevated levels of DHEAS (Moran, 1994, 1999; O'Driscoll, 1994). In turn, elevated androstenedione levels contribute to an increase in estrone levels through peripheral conversion of androgens to estrogens by aromatase.

Sex Hormone-Binding Globulin

Women with PCOS display decreased levels of sex hormone-binding globulin (SHBG). This glycoprotein, produced in the liver, binds most sex steroids. Only about 1 percent of these steroids are unbound and thus free and bioavailable. The synthesis of SHBG is suppressed by insulin as well as androgens, corticoids, progestins, and growth hormone (Bergh, 1993). Because of suppressed SHBG production, less circulating androgen is bound and thus more remains available to bind with end-organ receptors. It is for this reason that some women with PCOS will have total testosterone levels in the normal range, but will be clinically hyperandrogenic due to elevated free testosterone levels.

Anovulation

Although androgen levels are typically elevated in women with PCOS, progesterone levels are low due to anovulation. The precise mechanism leading to anovulation is unclear, but hypersecretion of LH has been implicated in menstrual irregularity. In addition, anovulation may result from insulin resistance, as a substantial number of anovulatory patients with PCOS may resume ovulatory cycles when treated with metformin, an insulin sensitizer (Nestler, 1998). Finally, the large antral follicle cohort may contribute to

anovulation. Some patients who have undergone ovarian wedge resection in the past, and more recently laparoscopic ovarian drilling, have found significant improvement in their menstrual regularity. One study demonstrated that 67 percent of PCOS patients developed regular menses following such surgery compared with 8 percent prior to surgery (Amer, 2002).

SIGNS AND SYMPTOMS

In women with PCOS, complaints stem from varied endocrine effects and may include menstrual irregularities, infertility, manifestations of androgen excess, or other endocrine dysfunction. Symptoms classically become apparent within a few years of puberty.

Menstrual Dysfunction

Menstrual dysfunction in women with PCOS may range from amenorrhea to oligomenorrhea to episodic menometrorrhagia with anemia. Chronic estrogen exposure unopposed by the effects of postovulatory progesterone produces constant mitogenic stimulation of the endometrium. The instability of the thickened endometrium results in an unpredictable bleeding pattern. Of note, androgens may counteract estrogen to produce an atrophic endometrium. It is therefore not uncommon to observe amenorrhea and a thin endometrial stripe in PCOS patients with elevated androgen levels.

Characteristically, oligomenorrhea (fewer than eight menstrual periods in 1 year) or amenorrhea (absence of menses for 3 or more consecutive months) with PCOS begins with menarche. However, approximately 50 percent of *all* postmenarchal girls have irregular periods for up to 2 years due to immaturity of the hypothalamic-pituitary-ovarian axis. In girls with PCOS, monthly ovulatory menstrual cycles are not established in the midteenage years, and they often continue to have irregular cycles.

Some evidence suggests that PCOS patients with prior irregular cycle intervals may develop regular cycle patterns as they age. A decreasing antral follicle cohort as women enter their 30s and 40s may lead to a concurrent decrease in androgen production (Elting, 2000).

Hyperandrogenism

Hyperandrogenism is typically manifested clinically by hirsutism, acne, and/or androgenic alopecia. In contrast, signs of virilization such as increased muscle mass, deepening of the voice, and clitoromegaly are not typical of PCOS. Virilization reflects higher androgen levels and should prompt investigation for an androgen-producing tumor of the ovary or the adrenal gland.

HIRSUTISM

In a female, hirsutism is defined as the presence of coarse, dark, terminal hairs distributed in a male pattern (Fig. 17-3). Hirsutism should be distinguished from hypertrichosis, which is a generalized increase in lanugo, that is, the soft, lightly pigmented hair associated with some medications and malignancies. Polycystic ovarian syndrome accounts for 70 to 80 percent of cases of hirsutism, with idiopathic hirsutism being the second most frequent cause (Azziz, 2003).

FIGURE 17-3

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photograph shows male pattern escutcheon.

Women with PCOS typically report hirsutism beginning in late adolescence or the early 20s. Additionally, a variety of drugs may also lead to hirsutism, and their use should be investigated (Table 17-3).

Table 17-3 Medications that May Cause Hirsutism and/or Hypertrichosis

Drug	Brand Name
Hirsutism	
Anabolic steroids	
Danazol	Danocrine
Metoclopramide	Reglan
Methyldopa	Aldomet
Phenothiazines	
Progestins	
Reserpine	Serpasil
Testosterone	
Hypertrichosis	

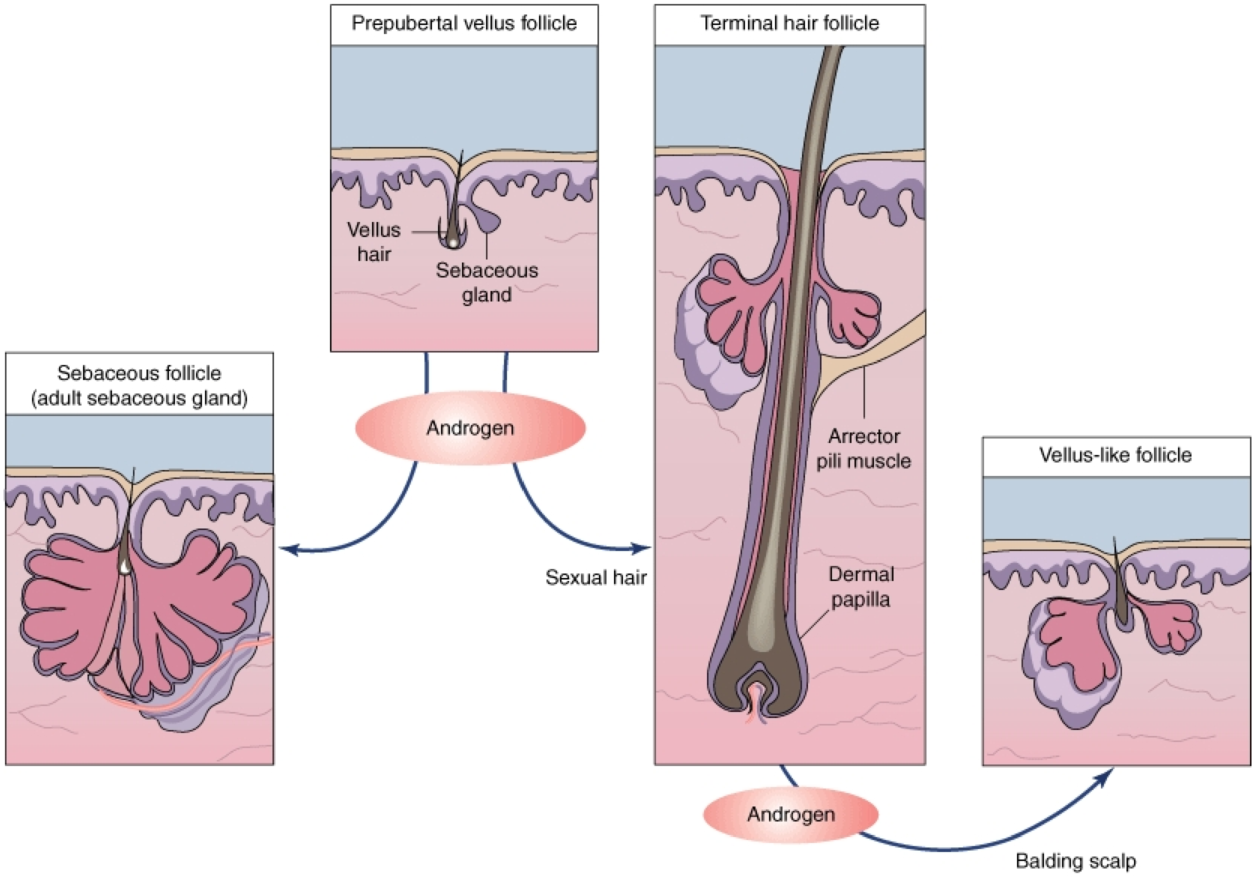
Cyclosporine	Sandimmune
Diazoxide	Hyperstat
Hydrocortisone	
Minoxidil	Rogaine
Penicillamine	Cuprimine
Phenytoin	Dilantin
Psoralens	Oxsoralen
Streptomycin	

From Leung, 1993, and Hunter, 2003, with permission.

Pathophysiology of Hirsutism

Elevated androgen levels play a major role in determining the type and distribution of hair (Archer, 2004). Within a hair follicle, testosterone is converted by the enzyme 5α-reductase to dihydrotestosterone (DHT) (Fig. 17-4). Although both testosterone and DHT convert short, soft vellus hair to coarse terminal hair, DHT is markedly more effective than testosterone. Conversion is irreversible, and only hairs in androgen-sensitive areas are changed in this manner to terminal hairs. As a result the most common areas affected with excess hair growth in women with PCOS include the upper lip, chin, sideburns, chest, and linea alba of the lower abdomen.

FIGURE 17-4

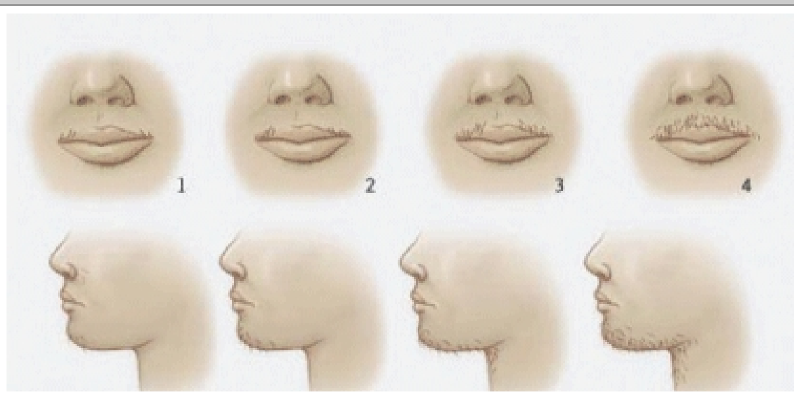


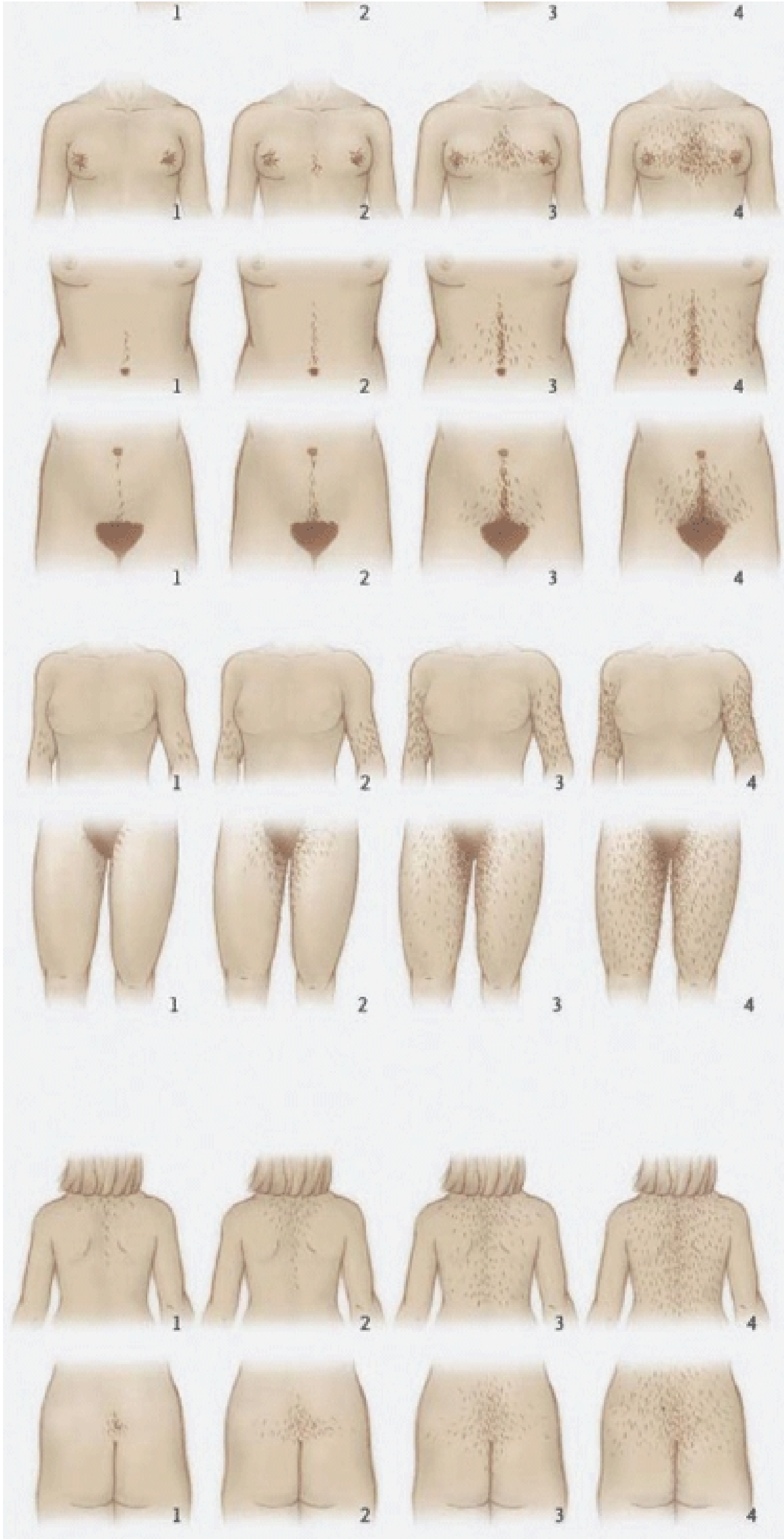
Androgenic effects on the pilosebaceous unit. In some hair-bearing areas, androgens stimulate sebaceous glands, and increased sebum may lead to acne. In other areas, vellus follicles respond to androgens and are converted to terminal follicles, leading to hirsutism. Under the influence of androgens, terminal hairs that were not previously dependent on androgens revert to a vellus form and balding results. *(From Rosenfield, 2005, with permission.)*

Ferriman-Gallwey Scoring System

To quantify the degree of hirsutism for research purposes, the Ferriman-Gallwey scoring system was developed in 1961 and later modified in 1981 (Ferriman, 1961; Hatch 1981). Within this system, abnormal hair distribution is assessed in nine body areas and scored from 0 to 4 (Fig. 17-5). Increasing numeric scores correspond to greater hair density within a given area. Many investigators define hirsutism as a score of 8 or greater using the modified version.

FIGURE 17-5





Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Depiction of the Ferriman-Gallwey system for scoring hirsutism. *(From Rosenfield, 2005, with permission.)*

This system is cumbersome and therefore is not used frequently in clinical settings. Nevertheless, it may be useful in following treatment responses in individual patients. Alternatively, many specialists choose to classify hirsutism more generally as mild, moderate, or severe depending on the location and density of hair growth.

Ethnicity

The concentration of hair follicles per unit area does not differ between men and women, however, racial and ethnic differences do exist. Individuals of Mediterranean descent have a higher concentration of hair follicles than Northern Europeans, and a much higher concentration than Asians (Speroff, 1999). For this reason, Asians with PCOS are much less likely to present with overt hirsutism than other ethnic groups. Additionally, there is also a strong familial tendency for the development of hirsutism, due to genetic differences in target tissue sensitivity to androgens and in the activity of 5α-reductase.

ACNE

Acne vulgaris is a frequent clinical finding in adolescents. However, acne that is particularly persistent or of late onset should suggest PCOS (Homburg, 2004). The prevalence of acne in women with PCOS is unknown, although one study found that 50 percent of adolescents with PCOS have moderate acne (Dramusic, 1997). In addition, an elevation of androgen levels has been reported in 80 percent of women with severe acne, 50 percent with moderate acne, and 33 percent with mild acne (Bunker, 1989). Women with moderate to severe acne have an increased prevalence (52 to 83 percent) of polycystic ovaries identified during sonographic examination (Betti, 1990; Bunker 1989; Jebraili, 1994).

Pathogenesis of Acne

The pathogenesis of acne vulgaris involves four factors, which include: blockage of the follicular opening by hyperkeratosis, sebum overproduction, proliferation of commensal *Propionibacterium acnes,* and inflammation (Purdy, 2006). In women with androgen excess, overstimulation of androgen receptors in the pilosebaceous unit results in increased sebum production that eventually leads to inflammation and comedone formation (see Fig. 17-4). Inflammation leads to the main long-term side effect of acneâ€”scarring. Accordingly, treatment is directed at lowering colonization of *P acnes,* minimizing inflammation, decreasing keratin production, and reducing androgen levels to diminish sebum production (Moghetti, 2006).

As in the hair follicle, testosterone is converted within sebaceous glands to its more active metabolite, DHT, by 5α-reductase. 5α-Reductase has two isoenzymes, type 1 and type 2. Of these, type 1 isoenzyme predominates in sebaceous glands. In skin types prone to acne, such as the face, the activity of type 1 isoenzyme is greater and implies that more DHT is being produced in these sebaceous glands (Thiboutot, 2004).

ALOPECIA

Female androgenic alopecia is a less common finding in women with PCOS. Hair loss progresses slowly and is characterized either by diffuse thinning at the crown with preservation of the frontal hairline or by bitemporal recession (Cela, 2003). Its pathogenesis involves an excess of 5α-reductase activity in the hair follicle leading to a rise in DHT levels. In addition, there is an increased expression of androgen receptors in these individuals (Chen, 2002).

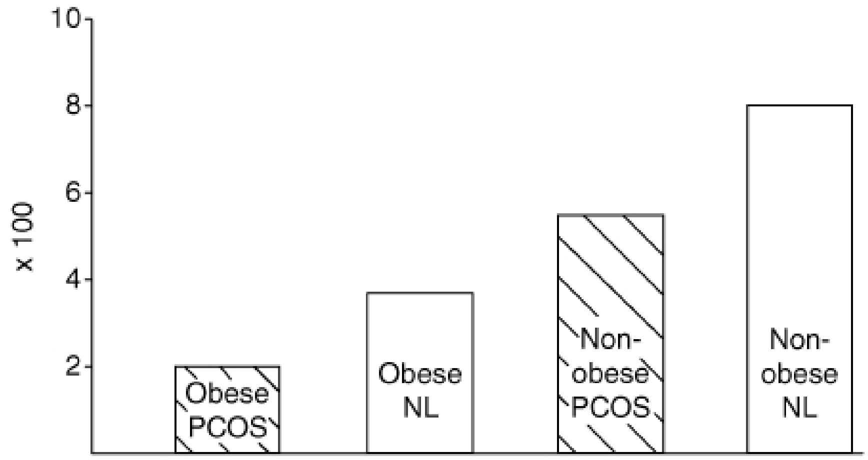
Alopecia, however, may reflect other serious disease. For this reason, affected women should also be evaluated to exclude thyroid dysfunction, anemia, or other chronic illness.

Other Endocrine Dysfunction

INSULIN RESISTANCE

Although not well characterized, the association between insulin resistance, hyperandrogenism, and PCOS has long been recognized. The precise incidence of insulin resistance in women with PCOS has been difficult to discern due to lack of a simple method for determining insulin sensitivity in an office setting. Although obesity is known to exacerbate insulin resistance, one classic study demonstrated that both lean and obese women with PCOS have increased rates of insulin resistance and type 2 diabetes mellitus (DM) compared with weight-matched controls without PCOS (Fig. 17-6) (Dunaif, 1989, 1992).

FIGURE 17-6



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Insulin sensitivity is decreased in obese women with polycystic ovarian syndrome. NL = normal (those without PCOS); PCOS = polycystic ovarian syndrome. *(Adapted from Dunaif, 1989, with permission.)*

Acanthosis Nigricans

This skin condition is characterized by thickened, gray-brown velvety plaques seen in areas of flexure such as the back of the neck, the axillae, the crease beneath the breast, the waist, and the groin (Fig. 17-7) (Panidis, 1995). Thought to be a cutaneous marker of insulin resistance, acanthosis nigricans may be found in individuals with or without PCOS. Insulin resistance leads to hyperinsulinemia, which is believed to stimulate keratinocyte and dermal fibroblast growth, producing the characteristic skin changes (Cruz, 1992). Acanthosis nigricans is more often found in obese women with PCOS (50 percent incidence) than those with PCOS and normal weight (5 to 10 percent). Less commonly, it is seen with genetic syndromes or malignancy of the gastrointestinal tract, such as adenocarcinoma of the stomach or pancreas (Torley, 2002).

FIGURE 17-7

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photograph shows acanthosis nigricans on the back of the neck.

Impaired Glucose Tolerance and Type 2 Diabetes Mellitus

Women with PCOS are at increased risk for impaired glucose tolerance (IGT) and type 2 DM. Based on oral glucose tolerance testing of obese women with PCOS, the prevalence of IGT and DM is approximately 30 percent and 7 percent, respectively (Legro, 1999). Similar findings were reported in a group of obese adolescents with PCOS (Palmert, 2002). In addition, β cell dysfunction that is independent of obesity has been reported in patients with PCOS (Dunaif, 1996a).

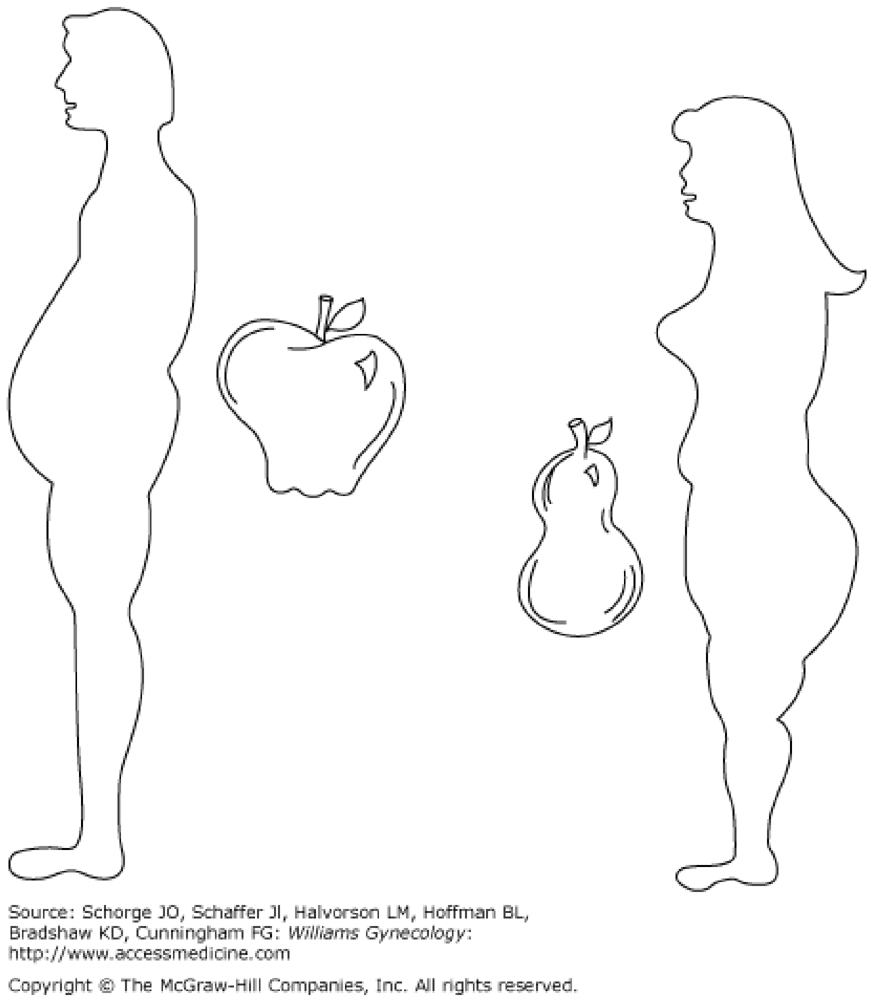
DYSLIPIDEMIA

The classic atherogenic lipoprotein profile seen in PCOS is characterized by elevated low-density lipoproteins (LDL), triglyceride levels, and total cholesterol:high-density lipoprotein (HDL) ratios, and by depressed HDL levels (Banaszewska, 2006). These changes may increase the risk of cardiovascular disease in women with PCOS independent of total cholesterol levels. Following criteria of the National Cholesterol Education Program, the prevalence of dyslipidemia in PCOS approaches 70 percent (Legro, 2001; Talbott, 1998).

OBESITY

Compared with age-matched controls, women with PCOS are more likely to be obese, as reflected by an elevated body mass index (BMI) and waist:hip ratio (Talbott, 1995). This ratio reflects an android or central pattern of obesity, which itself is an independent risk factor for cardiovascular disease (Fig. 17-8) (Nishizawa, 2002).

FIGURE 17-8



Obesity may present with a central distribution of body fat, also described in lay terms as an "apple-shaped" pattern. Alternatively, fat may predominate in the hips and buttocks in what is often termed a "pear-shaped" distribution.

As noted earlier, insulin resistance is believed to play a large role in the pathogenesis of PCOS and is often exacerbated by obesity (Dunaif, 1989). Thus, obesity can have a synergistic effect on PCOS and can worsen ovulatory dysfunction, hyperandrogenism, and the appearance of acanthosis nigricans.

Obstructive Sleep Apnea

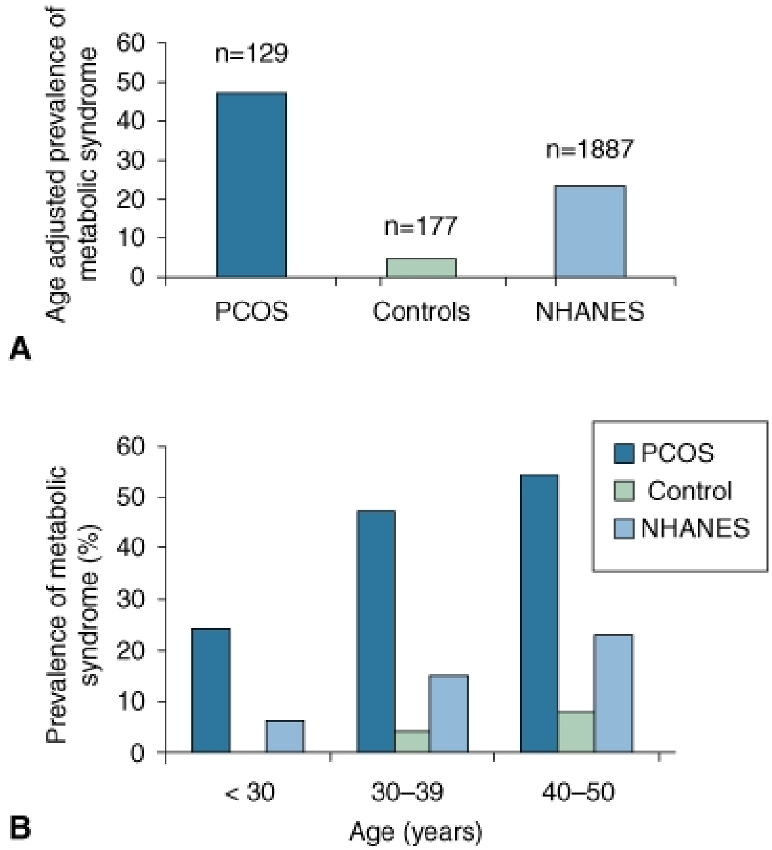
Obstructive sleep apnea is more common in women with PCOS and is likely related to central obesity and insulin resistance (Fogel, 2001; Vgontzas, 2001). However, some research has determined that the risk of sleep apnea is 30- to 40-fold higher in women with PCOS compared with weight-matched controls. This evidence points towards a link between obstructive sleep apnea and the metabolic and hormonal abnormalities associated with PCOS.

Metabolic Syndrome and Cardiovascular Disease

This syndrome is characterized by insulin resistance, obesity, atherogenic dyslipidemia, and hypertension. The metabolic syndrome is associated with an increased risk of cardiovascular disease (CVD) and type 2 DM (see Chap. 1, Metabolic Syndrome) (Schneider, 2006). The prevalence of metabolic syndrome is reported to be approximately 45 percent in women with PCOS compared with 4 percent in age-adjusted controls (Fig. 17-9) (Dokras, 2005). Polycystic ovarian syndrome shares several endocrine features with the metabolic syndrome, although definitive evidence for an increased incidence of CVD in women with PCOS is lacking (Legro,

1999; Talbott, 1998; Rebuffe-Scrive, 1989). However, in a small group of women with PCOS, Dahlgren and colleagues (1992) predicted a relative risk of myocardial infarction of 7.4. Another 10-year surveillance study showed an odds ratio of 5.91 for CVD in overweight Caucasian women with PCOS (Talbott, 1995). Thus, evidence suggests that women with PCOS should have CVD factors identified and treated (see Table 1-14) (Mosca, 2004).

FIGURE 17-9



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

A. Women with polycystic ovarian syndrome (PCOS) have an increased risk of metabolic syndrome compared with age-adjusted controls and with women from NHANES III. B. In women with PCOS, the risk of metabolic syndrome begins earlier than in controls or those from NHANES III. The Third National Health and Nutrition Survey (NHANES III) collected data from a representative sample of the noninstitutionalized civilian U.S. population from 1988 through 1994 (Ford, 2002). *(From Dokras, 2005, with permission.)*

In addition to components of the metabolic syndrome, other markers of subclinical disease link PCOS and CVD. Women with PCOS have been found to have a greater incidence of left ventricular diastolic dysfunction and increased internal and external carotid artery stiffness (Lakhani, 2000; Tiras, 1999). Moreover, in affected women, several studies have found greater endothelial dysfunction, which is described as an early event in the evolution of atherosclerosis (Diamanti-Kandarakis, 1999; Orio, 2004; Paradisi, 2003; Tarkun, 2004).

Endometrial Neoplasia

In women with PCOS, a threefold increased risk of endometrial cancer has been reported. Endometrial hyperplasia and endometrial cancer are long-term risks of chronic anovulation, and neoplastic changes in the endometrium are felt to arise from chronic unopposed estrogen (see Chap. 33) (Coulam, 1983). Moreover, the effects of hyperandrogenism and hyperinsulinemia to lower SHBG levels and increase circulating estrogen levels may add to this risk.

Few women who develop endometrial cancer are younger than 40 years, and most of these premenopausal women are obese or have chronic anovulation or both (Peterson, 1968; Rose, 1996). Thus, the American College of Obstetricians and Gynecologists (2000) recommends endometrial assessment in any woman older than 35 years with abnormal bleeding, and in those younger than 35 years who are suspected of having anovulatory uterine bleeding refractory to medical management (see Chap 8, Medical Treatment).

Infertility

Infertility or subfertility is a frequent complaint in women with PCOS and results from anovulatory cycles. Moreover, in women with infertility secondary to anovulation, PCOS is the most common cause and accounts for 80 to 90 percent of cases (Adams, 1986; Hull, 1987). Infertility evaluation and treatment in women with PCOS is described in more detail in Chapter 20, Ovulation Induction.

Pregnancy Loss

Women with PCOS who become pregnant are known to experience an increased rate (30 to 50 percent) of early miscarriage compared with a baseline rate of approximately 15 percent in the general population (Balen, 1993; Homburg, 1998b; Regan, 1990; Sagle, 1988; Schieve, 2003; Watson, 1993). The etiology of early miscarriage in women with PCOS is unclear. Initially, retrospective and observational studies showed an association between LH hypersecretion and miscarriage (Homburg, 1998a; Howles, 1987). However, one prospective study showed that lowering LH levels with GnRH agonists failed to show a benefit to this therapy (Clifford, 1997).

Others have suggested that insulin resistance is related to miscarriage in these women. To lower loss rates, an insulin level lowering drug, metformin (Glucophage, Bristol-Myers Squibb, New York, NY), has been investigated. Metformin, a biguanide, lowers serum insulin levels by reducing hepatic glucose production and increasing the sensitivity of liver, muscle, fat, and other tissues to the uptake and effects of insulin.

Several retrospective studies have indicated that women with PCOS taking metformin during pregnancy have a lower incidence of miscarriage (Glueck, 2001; Jakubowicz, 2002). In addition, a prospective study demonstrated a lower miscarriage rate for women conceiving while taking metformin compared with those using clomiphene citrate (Palomba, 2005). Similarly, another randomized trial demonstrated a reduced rate of pregnancy complications in women with PCOS using metformin during pregnancy compared with those given placebo (Vanky, 2004). However, until further randomized controlled trials are performed studying the effects of metformin (a category B drug) on pregnancy outcome, the use of this medication in gestation for miscarriage prevention is not recommended.

Complications in Pregnancy

Several pregnancy and neonatal complications have been associated with PCOS. One large meta-analysis found women with PCOS to have a two- to threefold higher risk of gestational diabetes, pregnancy-induced hypertension, preterm birth, and perinatal mortality, unrelated to multifetal gestations (Boomsma, 2006). In addition, many women with PCOS require the use of ovulation induction medications or in vitro fertilization, which substantially increases the risk of multifetal gestations and resultant increase in maternal and neonatal complications (see Chap. 20, Multifetal Gestation) (Fauser, 2005).

DIAGNOSIS

Polycystic ovarian syndrome is often referred to as a diagnosis of exclusion (Fig. 17-10). Thus, routine exclusion of other potentially serious disorders that may clinically appear like PCOS is warranted (Table 17-4).

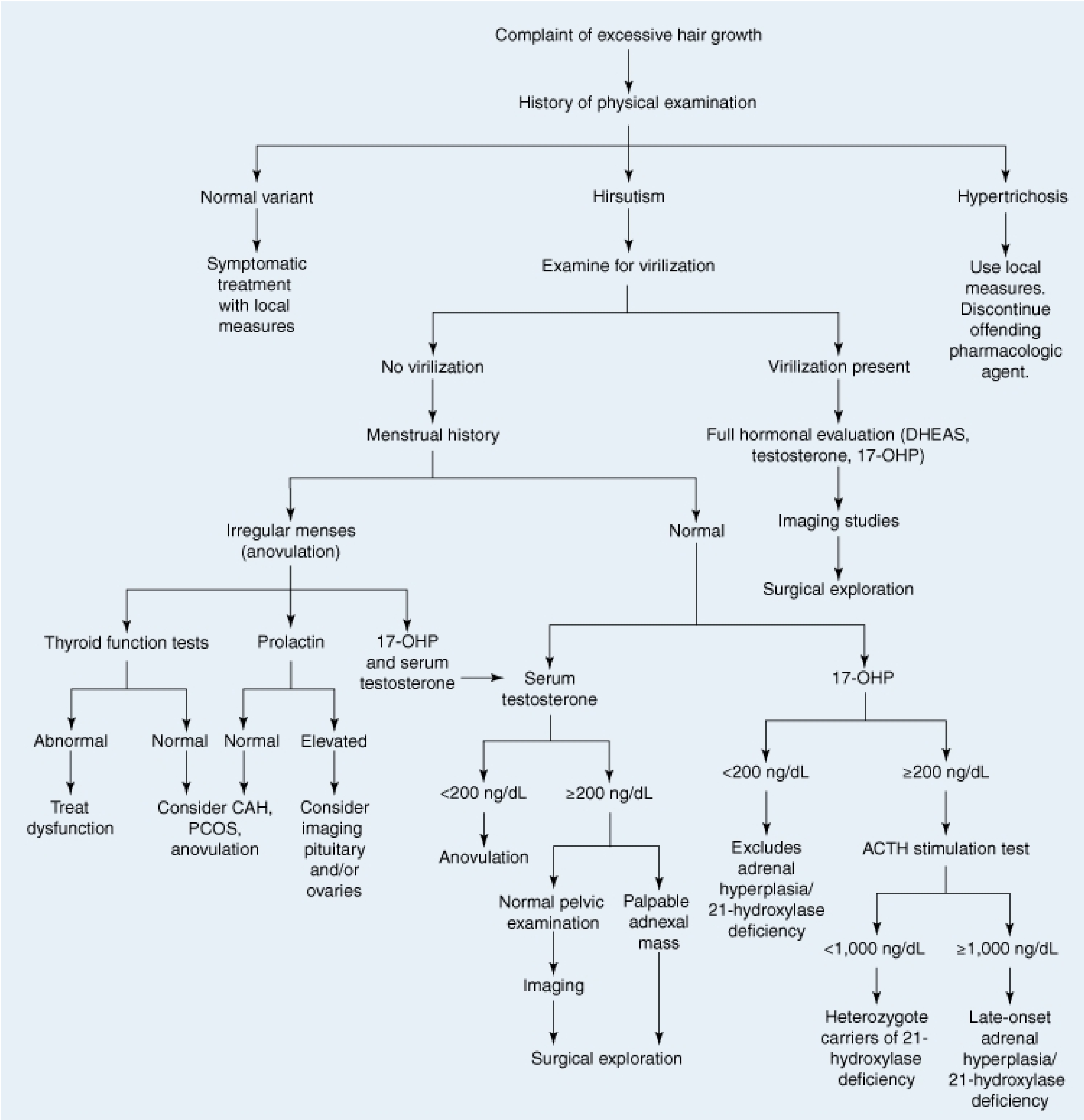
Table 17-4 Differential Diagnoses of Ovulatory Dysfunction and Hyperandrogenism

	Laboratory Testing	Indicative Results[a]
Causes of oligo- or anovulation		
PCOS	Testosterone level	Usually increased
	DHEAS level	May be mildly increased
	LH:FSH ratio	Typically greater than 2:1
Hyperthyroidism	TSH level	Decreased
Hypothyroidism		Increased
Hyperprolactinemia	PRL level	Increased
Hypogonadotropic hypogonadism	FSH, LH, E_2 levels	All decreased
POF	FSH, LH levels	Increased
	E_2 levels	Decreased
Causes of hyperandrogenism		
PCOS		
Late-onset CAH	17-OH-P level	>200 ng/dL
Androgen-secreting ovarian tumor	Total T level	>200 ng/dL
Androgen-secreting adrenal tumor	DHEAS level	>700 μg/dL
Cushing syndrome	Cortisol level	Increased
Exogenous androgen use	Toxicology screen	Increased

[a] Based on reference laboratory ranges of normal

CAH = congenital adrenal hyperplasia; DHEAS = dehydroepiandrosterone sulfate; E_2 = estradiol; FSH = follicle-stimulating hormone; LH = luteinizing hormone; 17-OH-P = 17-hydroxyprogesterone; PCOS = polycystic ovarian syndrome; POF = premature ovarian failure; PRL = prolactin; T = testosterone; TSH = thyroid-stimulating hormone.

FIGURE 17-10



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Algorithm for diagnosis of polycystic ovarian syndrome. ACTH = adrenocorticotropin hormone; CAH = congenital adrenal hyperplasia; DHEAS = dehydroepiandrosterone sulfate; PCOS = polycystic ovarian syndrome; 17-OHP = 17-hydroxyprogesterone. *(From Hunter, 2003, with permission.)*

Thyroid-Stimulating Hormone and Prolactin

Thyroid disease may frequently lead to menstrual dysfunction similar to that seen in women with PCOS (Chap. 8, Thyroid Disease). Accordingly, a serum TSH level is typically measured during evaluation. Similarly, hyperprolactinemia is a well-known cause of menstrual irregularities and occasionally amenorrhea. Elevated prolactin levels lead to anovulation through inhibition of GnRH

pulsatile secretion from the hypothalamus (see Chap. 15, Hyperprolactinemia).

Testosterone

Tumors of the ovary or adrenal are a rare but serious cause of androgen excess. A variety of ovarian neoplasms, both benign and malignant, may produce testosterone and lead to virilization. *Specifically, women with an abrupt onset, typically within several months, or sudden worsening of virilizing signs should prompt concern for a hormone-producing ovarian or adrenal tumor.* Symptoms may include deepening of the voice, frontal balding, severe acne or hirsutism or both, increased muscle mass, and clitoromegaly (Table 17-5). Accordingly, serum testosterone levels may be used to exclude these tumors (see Chap. 36).

Table 17-5 Clinical Features of Virilization
Hirsutism
Acne
Androgenic alopecia
Clitoromegaly
Deepening of the voice
Increased muscle mass
Decreased breast size
Amenorrhea

Free testosterone levels are more sensitive than total testosterone levels as an indicator of hyperandrogenism. Although improving, current free testosterone assays lack a uniform laboratory standard (Miller, 2004). For this reason, total testosterone levels remain the best approach for excluding a tumor. Threshold values beyond 200 ng/dL of total testosterone warrant evaluation for an ovarian lesion (Derksen, 1994).

Pelvic sonography is the preferred method to exclude an ovarian neoplasm in a female with very high androgen levels. Alternatively, computed tomography (CT) or magnetic resonance (MR) imaging may also be used in this setting.

Dehydroepiandrosterone Sulfate

Dehydroepiandrosterone sulfate is produced essentially exclusively by the adrenal gland. Therefore, serum DHEAS levels above 700 μg/dL are highly suggestive for the presence of an adrenal neoplasm. Adrenal imaging with abdominal CT or MR imaging is indicated for any patient with DHEAS levels that exceed this value.

Gonadotropins

During evaluation of amenorrhea, FSH and LH levels are typically measured to exclude premature ovarian failure and hypogonadotropic hypogonadism (see Table 17-4). Past this, however, LH and FSH levels have little additive value to the diagnosis of PCOS. Although classically LH levels measure at least twofold higher than FSH levels, this is not found in all women with PCOS. Specifically, one third of women with PCOS have circulating LH levels in the normal range, a finding more common in obese patients (Arroyo, 1997; Taylor, 1997). Moreover, serum LH levels are affected by sample timing within a menstrual cycle, use of oral contraceptive pills, and body mass index.

17-Hydroxyprogesterone

The term congenital adrenal hyperplasia (CAH) describes several autosomal recessive disorders that result from complete or partial deficiency of an enzyme involved in cortisol and aldosterone synthesis, usually 21-hydroxylase or less frequently 11-hydroxylase (see Fig. 15-13). Symptoms of CAH and their severity are varied. It may present in the neonate with ambiguous genitalia and life-threatening hypotension. Alternatively, symptoms may be milder and delayed until adolescence or adulthood. In this late-onset form of CAH, symptoms reflect accumulation of precursor C_{19} steroid hormones. These precursors are converted to

dehydroepiandrosterone, androstenedione, and testosterone, and signs of virilization predominate.

Specifically, deficiency of the most commonly affected enzyme, 21-hydroxylase, leads to accumulation of its substrate, 17-hydroxyprogesterone. Serum values are drawn in the morning from a fasting patient. Threshold values of 17-hydroxyprogesterone that measure more than 200 ng/dL should prompt an adrenocorticotropin hormone (ACTH) stimulation test. With this test, synthetic ACTH, 250 μg, is injected intravenously, and a serum 17-hydroxyprogesterone level is measured 1 hour later. Levels above 1000 ng/dL are indicative of late-onset CAH.

Cortisol

Cushing syndrome results from prolonged exposure to elevated levels of either endogenous or exogenous glucocorticoids. Of these, the syndrome is most frequently caused by administration of exogenous glucocorticoids. Alternatively, the term Cushing disease is reserved for cases of Cushing syndrome in which the constellation of symptoms stem from increased secretion of adrenocorticotropin hormone (ACTH) by a pituitary tumor. Individuals with Cushing syndrome may present with many symptoms suggestive of PCOS such as menstrual dysfunction, acne or hirsutism, truncal obesity, dyslipidemia, and glucose intolerance. Classically, moon facies and abdominal purple striae are also noted.

Initial laboratory testing is directed at confirming excessive glucocorticoid production. Analysis of a 24-hour urine collection for urinary free cortisol excretion is the preferred initial test. Normal values are less than 90 μg per 24 hours, and those in excess of 300 μg per day are considered diagnostic for Cushing syndrome (Kirk, 2000; Meier, 1997). Alternatively, a dexamethasone suppression test may be selected to avoid the difficulty of obtaining a 24-hour urine collection in some women. This, however, has a higher false-positive rate. One milligram of dexamethasone is taken orally at 11 pm, and a plasma cortisol level is measured at 8 am the following morning. Normal values are below 5 μg/dL (Crapo, 1979).

Measurements of Insulin Resistance and Dyslipidemia

Many women with PCOS have insulin resistance and compensatory hyperinsulinemia. Although the consensus meeting in Rotterdam suggested that tests of insulin resistance are *not* required to diagnose or treat PCOS, these tests are often used to evaluate glucose metabolism and impaired insulin secretion in these women (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004).

The gold standard for evaluating insulin resistance has been the hyperinsulinemic euglycemic clamp. Unfortunately, this test as well as the intravenous glucose tolerance test (IV GTT) requires an intravenous line and frequent sampling, are labor and time intensive, and are not practical in a clinical setting. Accordingly, other less sensitive surrogate markers that evaluate insulin resistance are used and include: (1) 2-hour glucose tolerance test (2-hr GTT), (2) fasting serum insulin level, (3) homeostasis model assessment of insulin resistance (HOMA IR), (4) quantitative insulin sensitivity check (QUICKI), and (5) calculation of serum glucose:insulin ratios.

Of these, a 2-hr GTT is frequently used to exclude impaired glucose tolerance (IGT) and type 2 DM, and is particularly important in obese PCOS patients who are at higher risk for both (Table 17-6). Over time, women with PCOS demonstrate a worsening of IGT, with a reported conversion rate of about 2 percent per year to type 2 DM. Measurements of fasting glucose and glycohemoglobin levels will not detect the early worsening of insulin resistance and glucose intolerance. This affirms the importance of periodic assessment of glucose tolerance with a 2-hr GTT in this population (Legro, 1999, 2005).

Table 17-6 Diagnosis of Impaired Glucose Tolerance and Diabetes Mellitus			
	Normal Range	**Impaired Glucose Tolerance**	**Diabetes Mellitus**
Fasting blood glucose level	≤100 mg/dL	100â€"125 mg/dL	≥126 mg/dL
2-hr GTT	≤140 mg/dL	140â€"199 mg/dL	≥200 mg/dL

2-hr GTT = 2-hour oral glucose tolerance test.

From Alberti, 1998, with permission.

In addition to assessment of insulin resistance, a fasting lipid profile is used to evaluate any signs of dyslipidemia.

Endometrial Biopsy

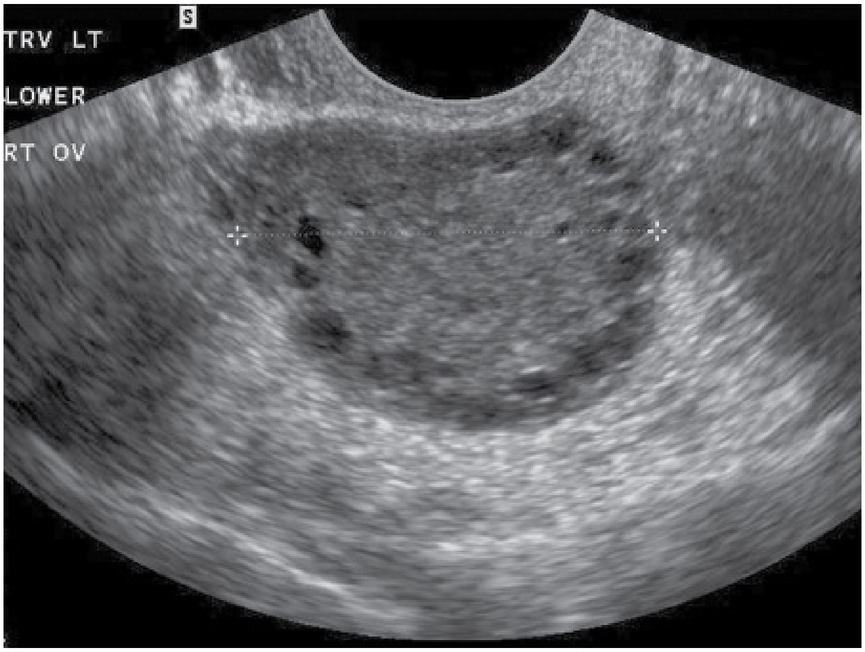
An endometrial biopsy is recommended in women older than age 35 with abnormal bleeding and in younger women with anovulatory bleeding refractory to hormonal treatment. Steps of this procedure are found in Chapter 8, Endometrial Biopsy.

Sonography

Histologically a polycystic ovary (PCO) displays increases in volume, number of ripening and atretic follicles, cortical stromal thickness, and number of hilar cell nests (Hughesdon, 1982). Many of these tissue changes can be seen sonographically, and a pelvic sonographic examination is commonly used to evaluate the ovaries in women with suspected PCOS. Sonography is particularly important for women with PCOS seeking fertility and in women with signs of virilization. A high-definition transvaginal approach is superior and has a higher detection rate of PCO than the transabdominal route. However, a transabdominal route is preferred for virginal adolescents.

Sonographic criteria for polycystic ovaries from the 2003 Rotterdam conference include ≥12 small cysts (2 to 9 mm in diameter) or an increased ovarian volume (>10 mL) or both (Fig. 17-11). Often there is an increased amount of stroma relative to the number of follicles (Balen, 2003). Only one ovary with these findings is sufficient to define PCOS. However, criteria do not apply to women taking combination oral contraceptive pills (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004).

FIGURE 17-11



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Transvaginal sonography displays multiple small hypoechoic cysts. *(Courtesy of Dr. Elysia Moschos.)*

In contrast, other findings are not valuable diagnostically. For example, the typical "black pearl necklace" appearance in which follicles are distributed just underneath the capsule in a row, and the perceived increase in stromal echogenicity have been eliminated as diagnostic criteria. Moreover, a polycystic ovary should not be confused with a multicystic ovary, which is normal size, contains six or more follicles without peripheral displacement, and lacks an increase in central stromal volume.

Remarkably, studies using sonography have shown that at least 23 percent of young women have ovaries that exhibit PCO morphology, yet many of these women have no other symptoms of PCOS (Clayton, 1992; Polson, 1988). In addition, a polycystic appearance of the ovaries can often be found in other conditions of androgen excess, such as congenital adrenal hyperplasia, Cushing syndrome, and exogenous use of androgenic medications. For this reason, PCO morphology found during sonographic examination is not used solely to make the diagnosis of PCOS.

TREATMENT

The choice of treatment for each symptom of PCOS depends on a woman's goals and the severity of endocrine dysfunction. Thus, anovulatory women desiring pregnancy will undergo a significantly different treatment than adolescents with menstrual irregularity and acne.

Observation

Women with PCOS who have fairly regular cycle intervals (8 to 12 menses per year) and mild hyperandrogenism may choose not to be treated. In these women, however, periodic screening for dyslipidemia and diabetes mellitus is warranted.

Weight Loss

For obese women with PCOS, lifestyle changes focused on diet and exercise are paramount to treatment at each stage of life. Even a modest amount of weight loss (5 percent of body weight) can result in restoration of normal ovulatory cycles in some women. This improvement results from reductions in insulin and androgen levels, the latter mediated through increases in SHBG levels (Huber-Buchholz, 1999; Kiddy, 1992; Pasquali, 1989).

The optimal diet that best improves insulin sensitivity is not known. Diets high in carbohydrates increase insulin secretion rates, whereas diets high in protein and fat lower those rates (Bass, 1993; Nuttall, 1985). However, very-high-protein diets are concerning with respect to stresses on kidney function. Moreover, they afford only short-term weight loss initially with lesser benefits over time (Legro, 1999; Skov, 1999). Thus, it appears that a well-balanced hypocaloric diet offers the most benefit in treating obese women with PCOS.

Exercise

Exercise is known to have a beneficial effect in treating patients with type 2 DM (Nestler, 1998). The most dramatic effect of lifestyle intervention was published in 2002 as the Diabetes Prevention Program. Women and men at risk for diabetes were asked to lose at least 7 percent of their weight and to exercise for 150 minutes each week. This group had a twofold greater benefit in delaying the onset of diabetes compared with a group given metformin alone. Both groups fared better than a placebo group (Knowler, 2002). Few studies, however, have looked specifically at the effect of exercise on insulin action in women with PCOS (Jaatinen, 1993).

Oligo-Ovulation and Anovulation

Women with oligo-ovulation or anovulation typically have fewer than eight menses per year, often skip menses for several months at a time, or simply have amenorrhea. Flow may be scanty or very long and heavy, resulting in anemia.

COMBINATION ORAL CONTRACEPTIVE PILLS

A first-line treatment for menstrual irregularities is combination oral contraceptive pills (COCs), which will induce regular menstrual cycles. In addition, COCs reduce androgen levels. Specifically, COCs suppress gonadotropin release, which results in decreased ovarian androgen production. Moreover, the estrogen component increases SHBG levels. The progestin component antagonizes the endometrial proliferative effect of estrogen, thus reducing risks of endometrial hyperplasia due to unopposed estrogen.

Theoretically, progestin-containing pills that contain norethindrone; a third-generation progestin, such as norgestimate or desogestrel; or the newer progestin, drospirenone, are preferred to COCs containing progestins with more androgenic properties. However, no pill has shown superiority compared with another in reducing hirsutism (Sobbrio, 1990). Alternative combination hormonal options include the contraceptive patch and vaginal ring (see Chap. 5, Transdermal Administration).

In initiating therapy, if a woman's last menses was more than 4 weeks prior, a pregnancy test is indicated. If negative, progesterone is given to produce a withdrawal bleed prior to COC initiation. Typical regimens include: medroxyprogesterone acetate (MPA) (Provera, Pfizer, New York, NY), 10 mg orally daily for 10 days; MPA, 10 mg orally twice daily for 5 days; or micronized progesterone (Prometrium, Solvay Pharmaceuticals, Marietta, GA), 200 mg orally daily for 10 days.

CYCLIC PROGESTINS

In patients who are not candidates for combination hormonal contraception, progesterone withdrawal is recommended every 1 to 3 months. Examples of regimens used include: MPA, 5 to 10 mg orally daily day for 12 days, or micronized progesterone, 200 mg orally each evening for 12 days. Patients should be counseled that intermittent progestins will not reduce symptoms of acne or hirsutism nor provide contraception.

INSULIN-SENSITIZING AGENTS

Although the use of insulin sensitizers in PCOS has not been approved by the Food and Drug Administration (FDA), they have been found to be increasingly beneficial for both metabolic and gynecologic issues. For example, metformin may be used to treat women with infertility and PCOS. This drug improves peripheral insulin sensitivity by reducing hepatic glucose production and increasing target tissue sensitivity to insulin. Metformin decreases androgens in both lean and obese women, leading to increased rates of spontaneous ovulation (Batukan, 2001; Essah, 2006; Haas, 2003; Kocak, 2002; Lord, 2003).

A number of studies have demonstrated that up to 40 percent of anovulatory women with PCOS will ovulate, and many will achieve pregnancy with metformin alone. (Diamanti-Kandarakis, 1998; Fleming, 2002; Neveu, 2007; Velazquez, 1997). Metformin is a category B drug and is safe to use as an ovulatory induction agent. As such, it may be used alone or in concert with other medications such as clomiphene citrate (see Chap. 20, Ovulation Induction). Specifically, metformin has been shown to increase

the ovulatory response to clomiphene citrate in patients who were previously clomiphene-resistant (Nestler, 1998). Despite these positive findings regarding metformin and ovulation induction, Legro and colleagues (2007) in a randomized prospective study of 626 women found higher live-birth rates with clomiphene citrate alone (22 percent) than with metformin alone (7 percent).

A rare adverse side effect of metformin is lactic acidosis and is almost exclusively found in patients with renal insufficiency, liver disease, or congestive heart failure. More common side effects are gastrointestinal, and these can be minimized by starting at a low dose and gradually increasing the dose over several weeks to an optimal level. In clinical studies, 1500 to 2000 mg in divided doses daily with meals are typically used.

The thiazolidinediones are another class of medications also used for patients with diabetes mellitus and include rosiglitazone (Avandia, GlaxoSmithKline, Philadelphia, PA) and pioglitazone (Actos, Takeda Pharmaceuticals, Deerfield, IL). These agents bind to insulin receptors on cells throughout the body, causing them to become more responsive to insulin and thereby lowering serum glucose and insulin levels. Similar to metformin, rosiglitazone and pioglitazone have been shown to improve ovulation in some patients (Azziz, 2001; Dunaif, 1996b; Ehrmann, 1997). However, the glitazones are category C drugs and thus should be used as ovulation induction agents in rare cases and discontinued once pregnancy is achieved.

Hirsutism

In the treatment of hirsutism, a primary goal is lowering androgen levels to halt further conversion of vellus hairs to terminal ones. However, medical therapies will not eliminate abnormal hair growth already present. Moreover, treatments may require 6 to 12 months before clinical improvement is apparent. For this reason, clinicians should be familiar with temporary hair removal methods that may be used in the interim. Permanent cosmetic therapies may then be implemented once medications have reached maximal therapeutic effect.

COMBINATION ORAL CONTRACEPTIVES

As described earlier, COCs are effective in establishing regular menses and lowering ovarian androgen production. As an additional effect, the estrogen component of these pills leads to increased SHBG levels. With higher SHBG levels, a greater amount of free testosterone is bound and thus becomes biologically unavailable at the hair follicle.

GONADOTROPIN-RELEASING HORMONE AGONISTS

As described in Chapter 9, GnRH Agonists, gonadotropin-releasing hormone (GnRH) agonists effectively lower gonadotropin levels over time, and in turn subsequently lower androgen levels. Despite their effectiveness in treating hirsutism, administration of these agents is not a preferred long-term treatment method due to associated bone loss, high cost, and menopausal side effects.

EFLORNITHINE HYDROCHLORIDE

This antimetabolite topical cream is applied twice daily to areas of facial hirsutism and is an irreversible inhibitor of ornithine decarboxylase. This enzyme is necessary for hair follicle cell division and function, and its inhibition results in slower hair growth. It does not permanently remove hair, and thus women are required to continue routine methods of hair removal while using this medicine.

Clinical results from eflornithine hydrochloride (Vaniqa, SkinMedica, Carlsbad, CA) may require 4 to 8 weeks of use. However, clinical trials have shown that approximately one third of patients have marked improvement after 24 weeks of eflornithine use compared with placebo, and 58 percent showed some overall improvement in hirsutism scores (Balfour, 2001).

ANDROGEN-RECEPTOR ANTAGONISTS

Antiandrogens are competitive inhibitors of androgen binding to the androgen receptor (Farquhar, 2003; Moghetti, 2000; Venturoli, 1999). Although these agents are effective in the treatment of hirsutism, they carry a risk for several side effects. Metrorrhagia may frequently develop. In addition, as antiandrogens, these drugs bear a theoretical risk of pseudohermaphroditism in male fetuses of women using such medications in early pregnancy. Accordingly, these drugs are commonly used in conjunction with oral contraceptive pills, which prompt regular menses and provide effective contraception.

None of the antiandrogen agents are approved by the FDA for treatment of hyperandrogenism and thus are used off-label.

Spironolactone (Aldactone, Pfizer, New York, NY), in a dosage of 50 to 100 mg orally twice daily is the primary antiandrogen used currently in the United States. In addition to its antiandrogen effects, this drug also affects hair conversion through its direct inhibition of 5α-reductase. Spironolactone is also a potassium-sparing diuretic. As such, it should not be prescribed for chronic use in combination with agents that can also raise blood potassium levels, such as potassium supplements, angiotensin-converting enzyme (ACE) inhibitors, nonsteroidal anti-inflammatory drugs such as indomethacin, or other potassium-sparing diuretics.

In Europe, Canada, and Mexico, the preferred antiandrogen is cyproterone acetate, usually marketed in an oral contraceptive pill. However, this agent is not approved by the FDA (Van der Spuy, 2003). Flutamide is another nonsteroidal antiandrogen marketed for the treatment of prostate cancer, but is rarely used for hirsutism due its potential hepatotoxicity.

5α-REDUCTASE INHIBITORS

Conversion of testosterone to DHT may be effectively decreased by the 5α-reductase inhibitor finasteride. This drug is available as a 5-mg tablet for prostate cancer (Proscar, Merck, Whitehouse Station, NJ) and a 1-mg tablet for the treatment of male alopecia (Propecia, Merck). Most studies have used 5-mg daily doses and have found finasteride to be modestly effective in the treatment of hirsutism (Fruzzetti, 1994; Moghetti, 1994).

Side effects are low with finasteride, although decreased libido has been noted. However, as with other antiandrogens, the risk of male fetal teratogenicity is present, and effective contraception must be used concurrently.

HAIR REMOVAL

Hirsutism is often treated by mechanical means, and these include both depilation and epilation techniques. In addition to hair removal, lightening hair color with bleach is an additional cosmetic option.

Depilation

Depilation describes hair removal above the skin surface. Shaving is the most common form and does not exacerbate hirsutism, contrary to the myth that it will increase hair follicle density. Alternatively, topical chemical depilatories are also effective. Available in gel, cream, lotion, aerosol, and roll-on forms, these agents contain calcium thioglycolate, which breaks disulfide bonds between hair protein chains causing hair to breakdown and separate easily from the skin surface.

EPILATION

Mechanical Removal

In contrast to depilation, epilation removes the entire hair shaft and root, and includes techniques such as plucking, waxing, threading, electrolysis, and laser treatment. Threading, also known as "khite" in Arabic, is a fast method for removing entire hairs and is commonly used in the Middle East and India. Hairs are snared within a outstretchedstrand of a twisted cotton thread and pulled out.

Thermal Destruction

Although waxing and plucking allow effective temporary hair removal, permanent epilation may be achieved with thermal destruction of the hair follicle. Electrolysis, performed by a trained individual, involves placement of a fine electrode and passage of electric current to destroy individual follicles. It requires repetitive treatments over several weeks to months, can be painful, and may result in scarring.

Alternatively, laser therapy uses specific laser wavelengths to permanently destroy follicles. During this process, termed *selective photothermolysis,* only target tissues absorb laser light and are heated. Surrounding tissues fail to absorb the selective wavelength and receive minimal thermal damage. For this reason, light-skinned women with dark hairs are better candidates for laser treatment due to the selective wavelength absorption by their hair.

Advantageously, laser treatment can cover a wider surface area than electrolysis and therefore requires fewer treatments. It causes less pain, but is expensive and can result in dyspigmentation.

Prior to any epilation technique, topical anesthetics may be prescribed. Specifically, a topical cream combination of 2.5-percent lidocaine and 2.5-percent prilocaine (EMLA cream, AstraZeneca, Wilmington, DE) can be applied as a thick layer that remains for 5

to 10 minutes and is removed just prior to epilation. Recommended adult dosing is 2.5 g per 2 x 2-inch area of skin treated.

Acne

One part of acne treatment is similar to that for hirsutism and involves lowering of androgen levels. Therapy may include: (1) combination oral contraceptive pills; (2) antiandrogens such as spironolactone or flutamide, which inhibit binding of androgen to its receptor; or (3) 5¤-reductase inhibitors such as finasteride.

In addition to lowering androgen levels, other therapies may be added. For this reason, women with moderate to severe acne may benefit from consultation with a dermatologist (Table 17-7).

Table 17-7 Algorithm of Acne Treatment

	Mild		**Moderate**		
Therapy	**Comedonal**	**Papular/Pustular**	**Papular/Pustular**	**Nodular**	**Severe, Nodular**
First-line therapy	T. retinoid	T. retinoid + BPO or BPO/AB	T. retinoid + oral antibiotic + BPO or BPO/AB	T. retinoid + oral antibiotic Â± BPO or BPO/AB	Oral isotretinoin
Alternatives	Salicylic acid			Oral isotretinoin	Oral antibiotic + T. retinoid + BPO or BPO/AB
Alternatives for female patients			Hormonal therapy + T. retinoid Â± BPO or BPO/AB	Hormonal therapy + T. retinoid Â± BPO or BPO/AB	Hormonal therapy + oral antibiotic + T. retinoid Â± BPO or BPO/AB
Maintenance therapy	T. retinoid Â± BPO or BPO/AB		T. retinoid Â± BPO or BPO/AB		T. retinoid Â± BPO or BPO/AB

AB = topical antibiotic; BPO = benzoyl peroxide; BPO/AB = benzoyl peroxide and topical antibiotic combination agent; T. retinoid = topical retinoid.

From Zaenglein, 2006, with permission.

TOPICAL AND SYSTEMIC ANTIBIOTICS

Topical antibiotics typically include erythromycin and clindamycin, whereas oral antibiotics most often used for acne include doxycycline, minocycline, and erythromycin. Oral antibiotics are more effective than topical therapies, but can have a variety of side effects such as sun sensitivity and gastrointestinal upset.

TOPICAL BENZOYL PEROXIDE

Benzoyl peroxide is an excellent antimicrobial and anti-inflammatory agent. It is the active ingredient in many over-the-counter products used for acne. Some prescription products also combine 5-percent benzoyl peroxide with antibiotics such as clindamycin or erythromycin.

TOPICAL RETINOIDS

Derived from vitamin A, topical retinoids regulate the follicular keratinocyte and normalize its desquamation. In addition, this group of agents also has direct anti-inflammatory properties, and thereby targets two factors linked to acne vulgaris (Table 17-8) (Zaenglein, 2006). The most commonly used agent with retinoid activity is tretinoin (Retin-A Micro, Ortho Dermatological, Skillman, NJ; Avita, Mylan Pharmaceuticals, Morgantown, WV), although adapalene (Differin, Galderma Laboratories, Fort Worth, TX) and tazarotene (Tazorac, Allergen, Irvine CA) have also been shown to be effective (Gold, 2006; Leyden, 2006). Initially, a pea-sized dab sufficient to cover the entire face is applied every third night and progressively increased as tolerated to nightly

application (Krowchuk, 2005). Tretinoin may cause a transient worsening of acne during the first weeks of treatment.

Table 17-8 Topical Retinoids

Retinoid	Formulation	Strength (%)
Tretinoin	Cream	0.025, 0.05, 0.1
	Gel	0.01, 0.025
	Liquid	0.05
	Microsphere gel (Retin-A Micro)	0.04, 0.1
	Polymerized cream (Avita)	0.025
	Polymerized gel (Avita)	0.025
Adapalene (Differin)	Cream	0.1
	Gel	0.1
	Solution	0.1
Tazarotene (Tazorac)	Cream	0.05, 0.1[a]
	Gel	0.05, 0.1[a]

[a] Indicated for psoriasis.

From Zaenglein, 2006, with permission.

Concerning teratogenicity, tretinoin and adapalene are category C drugs and thus are not recommended for use during pregnancy or breast feeding. However, epidemiologic studies currently do not support a link between topical retinoids and birth defects (Jick, 1993; Loureiro, 2005). Tazarotene is category X and similarly should not be used during these times.

ISOTRETINOIN

Oral isotretinoin (Accutane, Roche Pharmaceuticals, Nutley, NJ) is an analog of vitamin A that is highly effective for the treatment of severe recalcitrant acne. Despite its efficacy, oral isotretinoin is teratogenic if taken during the first trimester of pregnancy. Malformations typically involve the cranium, face, heart, central nervous system, and thymus. Therefore isotretinoin administration should be limited to women using a reliable form of contraception.

Acanthosis Nigricans

Optimal treatment for acanthosis nigricans should be directed towards decreasing insulin resistance and hyperinsulinemia (Field, 1961). Specifically, a few studies have shown an improvement in acanthosis nigricans with insulin sensitizers (Walling, 2003). Other methods, including topical antibiotics, topical and systemic retinoids, keratolytics, and topical corticosteroids have been tried with limited success (Schwartz, 1994).

Surgical Therapy

Although ovarian wedge resection is now rarely performed, laparoscopic ovarian drilling has been shown to restore ovulation in a significant number of women with PCOS that were found to be resistant to clomiphene citrate (see Section 41-32, Ovarian Drilling) (Hendriks, 2007).

Rarely, oophorectomy is a viable option for women not seeking fertility who exhibit signs and symptoms of ovarian hyperthecosis

and accompanying severe hyperandrogenism. Ovarian and adrenal androgen-secreting neoplasms should be treated surgically (see Chap. 36).

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ANATOMIC DISORDERS: INTRODUCTION

Anatomic disorders of the female reproductive system occur frequently and may result from genetic mutation, developmental arrest, or environmental insults that may exert their effects at critical stages of embryonic development. Disorders range from congenital absence of the vagina and uterus, to defects in lateral or vertical fusion of the mÃ¼llerian ducts, to the formation of external genitalia that are ambiguous in sexual differentiation. A variety of anatomic defects may also be found in the urinary excretory system. Because of the intertwined development of these two systems, organs from both are commonly involved in urogenital tract disorders.

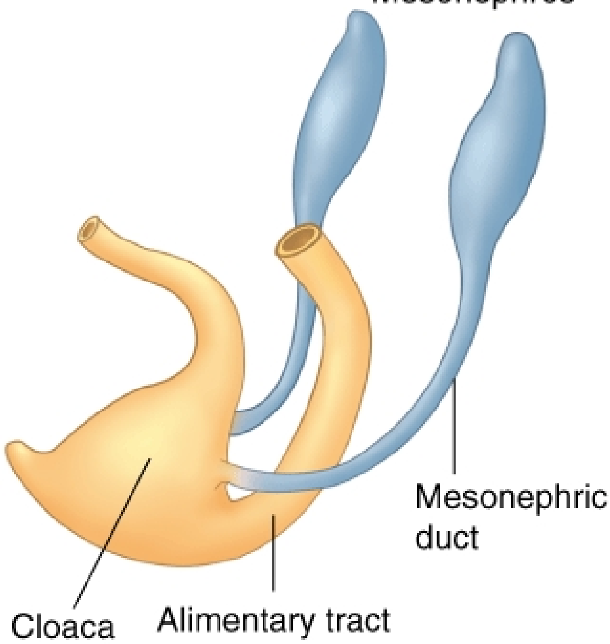
NORMAL EMBRYOLOGY

Overview

A basic comprehension of the rather complex embryology of the reproductive system aids in clarifying the nature of various malformations and in understanding their association with other genitourinary anomalies (Shatzkes, 1991). The urogenital system is functionally divided into the urinary system and the genital system. The urinary organs include the kidney, the ureters, the bladder, and the urethra. The reproductive organs consist of the gonads, the ductal system, and the external genitalia. Like most organ systems, urogenital tract development involves a complex interplay of multiple cell types, and it occurs during a relatively narrow time window. The temporal pattern of gene expression and the spatial relationships of the developing tissues is vitally important for normal development (Park, 2005).

Both the urinary and genital systems develop from the intermediate mesoderm, which extends along the entire length of the embryo (Moore, 1988). During initial folding of the embryo in the horizontal plane, a longitudinal ridge of this intermediate mesoderm develops along each side of the primitive abdominal aorta and is called the urogenital ridge. The urogenital ridge then differentiates into the nephrogenic and genital ridges. The genital ridges develop into the primordial gonads and are discussed in the next section. The nephrogenic ridges instead give rise to the paired mesonephric ducts, also termed wolffian ducts. These ducts connect the mesonephric kidneys to the cloaca, which is a common opening into which the embryonic urinary, genital, and alimentary tracts join (Fig. 18-1A).

FIGURE 18-1



A

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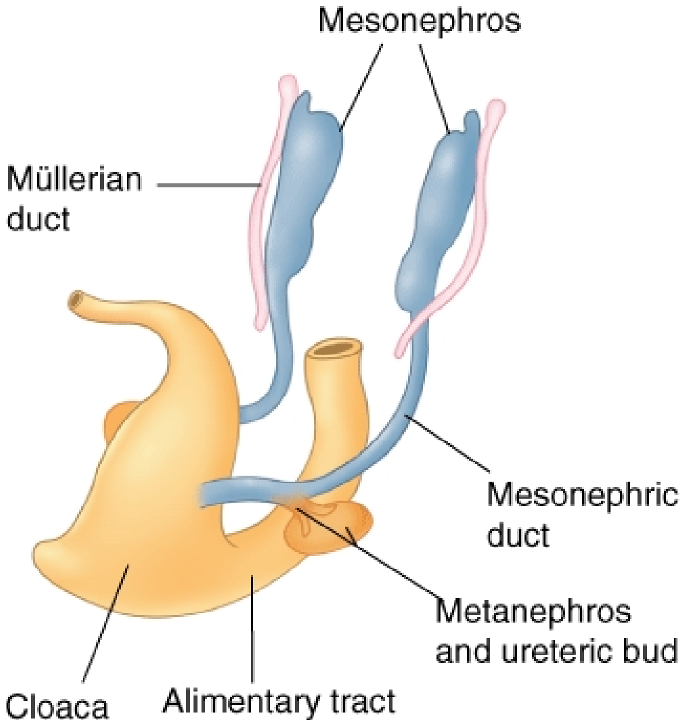

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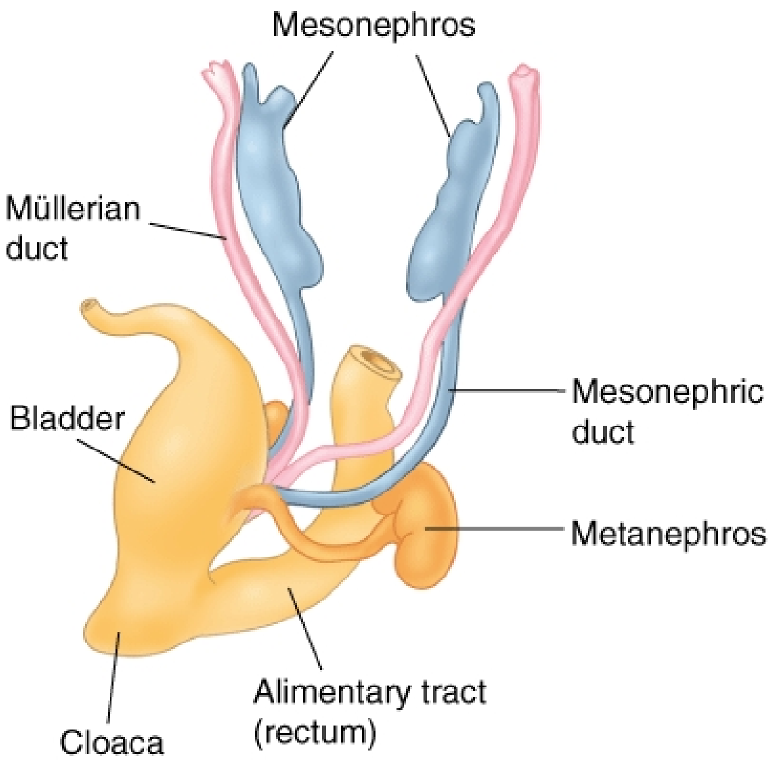

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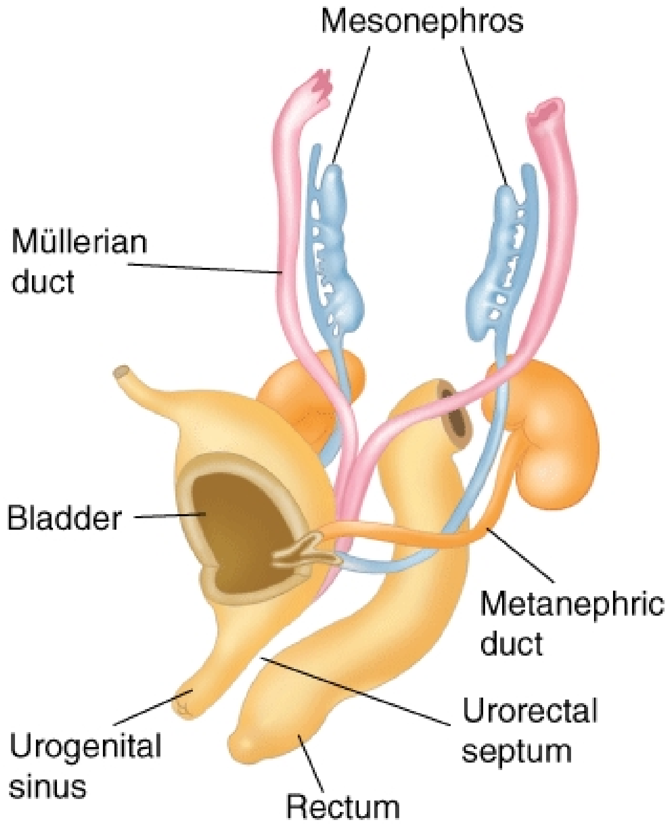

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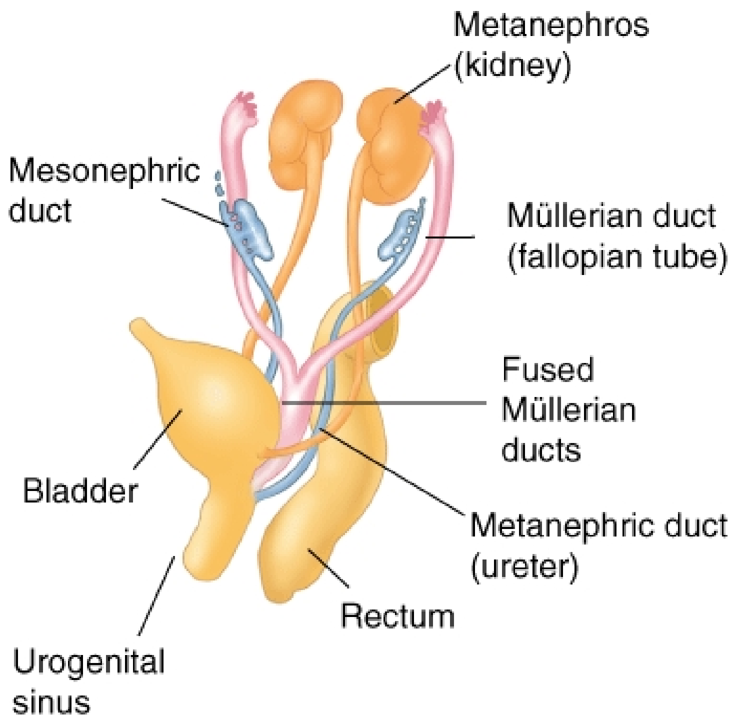

E

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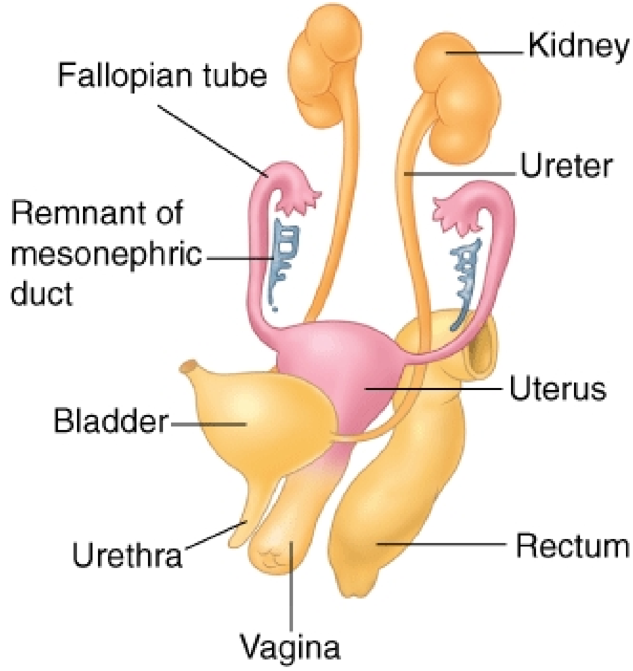


F

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Embryonic development of the female genitourinary tract. *(From Schatzkes, 1991, with permission.)*

Recall that evolution of the renal system passes sequentially through the pronephric and mesonephric stages to reach the permanent metanephric system. The ureteric bud arises from the mesonephric duct at approximately the fifth week of fetal life. It lengthens to become the metanephric duct (ureter) and induces differentiation of the metanephros, which will eventually become the final functional kidney after degeneration of the mesonephric kidney at 10 weeks (Fig. 18-1B).

The paired paramesonephric, also known as mÃ¼llerian ducts, develop from an invagination of the coelomic epithelium at about the sixth week, and grow on either side between the developing gonad and mesonephric duct. The caudal portions of the mÃ¼llerian ducts approximate one another in the midline and end behind the cloaca near the mesonephric ducts (Fig. 18-1C). The cloaca is divided by formation of the urorectal septum by the seventh week and is separated to create the rectum and the urogenital sinus (Fig. 18-1D). The urogenital sinus is considered in three parts (1) the cephalad or vesicle portion, which will form the urinary bladder (2) the middle or pelvic portion, which creates the female urethra; and (3) the caudal or phallic part, which will give rise to the distal vagina and the greater vestibular (Bartholin), urethral, and paraurethral (Skene) glands. During differentiation of the urinary bladder, the caudal portion of the mesonephric ducts is incorporated into the trigone portion of the bladder wall. Consequently, the caudal portion of the metanephric ducts (ureters) penetrates the bladder with distinct and separate orifices (Fig. 18-1D).

The close association between the mesonephric (wolffian) and paramesonephric (mÃ¼llerian) ducts has important clinical relevance because developmental insult to either system is often associated with anomalies that involve the kidney, ureter, and the reproductive tract. For example, Kenney and colleagues (1984) showed that up to 50 percent of females with uterovaginal malformations have associated urinary tract anomalies.

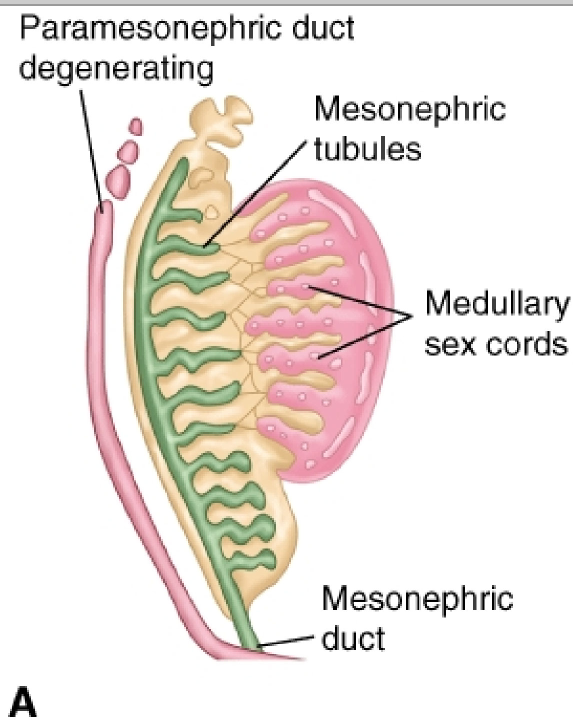
Gonadal Differentiation

Although the gonads and reproductive tract complete their final maturation during puberty, critical developmental steps occur during the embryonic and fetal periods. Histologically, the genital ridge begins as coelomic epithelium with underlying mesenchyme. The major cellular components of the genital ridge include the primordial germ cells and somatic cells. In both 46,XX and 46,XY embryos, the primordial germ cells are first identified as large polyhedral cells in the yolk sac. These cells migrate by ameboid motion to the dorsal mesentery and then onto the undifferentiated genital ridge.

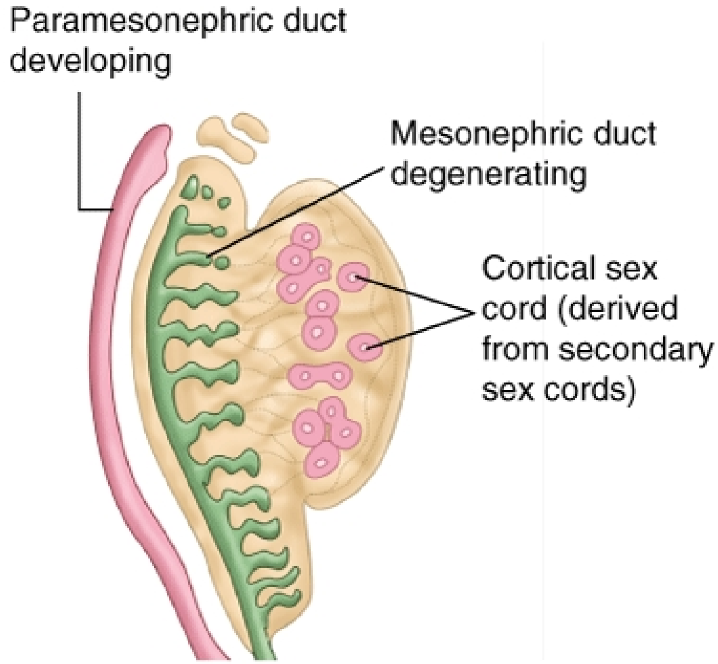
The embryonic reproductive tract is capable of developing along either male or female lines. From this point onward, the presence or absence of gonadal determinant genes determines fetal gender development (Taylor, 2000). Sexual differentiation is dependent upon the genetic sex that is determined at fertilization of the X-bearing oocyte by either an X- or Y-chromosome-bearing sperm. In the presence of the sex-determining region of the Y (SRY) locus on the Y chromosome, the gonads develop as testes. Other important gonadal development factors include SF-1, SOX 9, WT1, WNT4, and DAX-1 (Viger, 2005). Other key factors have been described and are known to act at the transcriptional level (Park, 2005).

In males, cells in the medullary region of the primitive sex cord differentiate into Sertoli cells, and these cells organize to form the testicular cords (Fig. 18-2). Testicular cords are identifiable at 6 weeks and consist of these Sertoli cells and tightly packed germ cells. Early in the second trimester, the cords develop a lumen and become seminiferous tubules. Development of a testis-specific vasculature is crucial for normal testicular development (Ross, 2005).

FIGURE 18-2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



B

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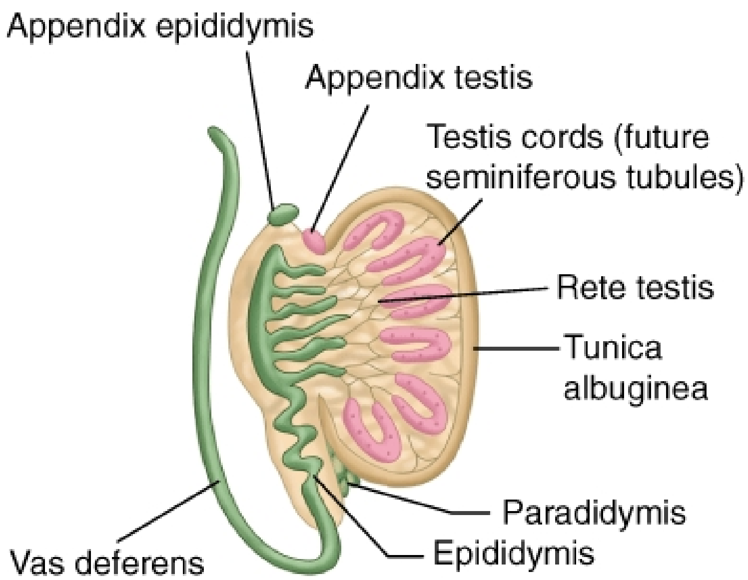
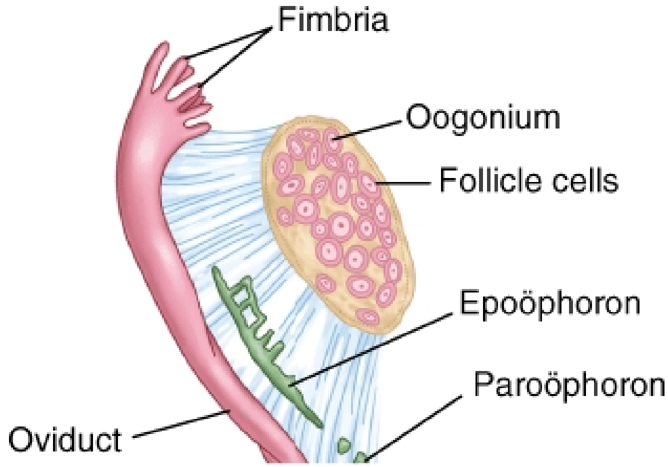


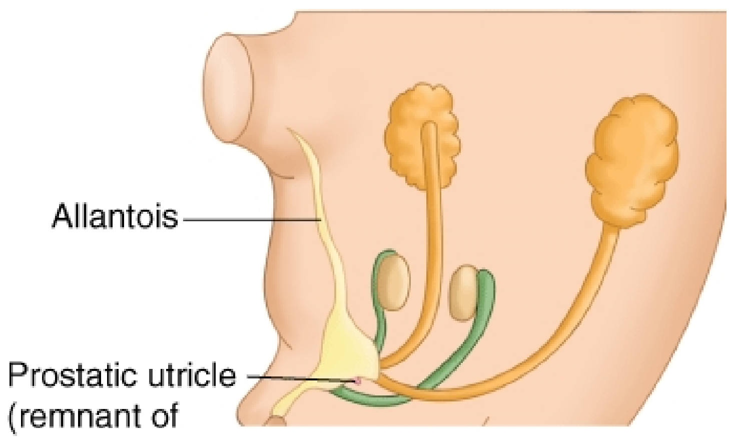
C

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



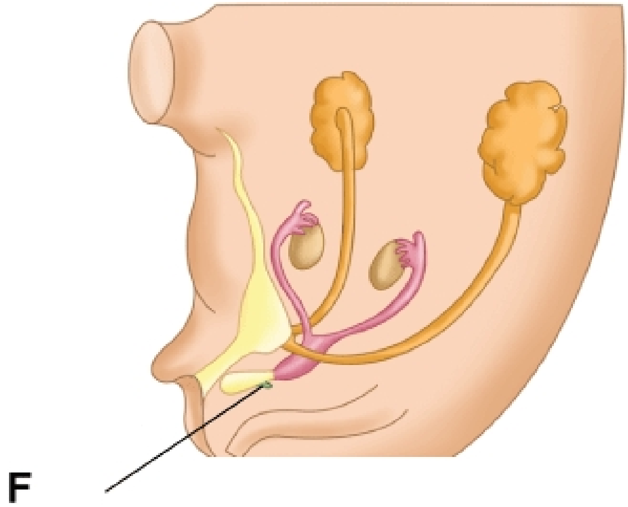
D

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



E

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

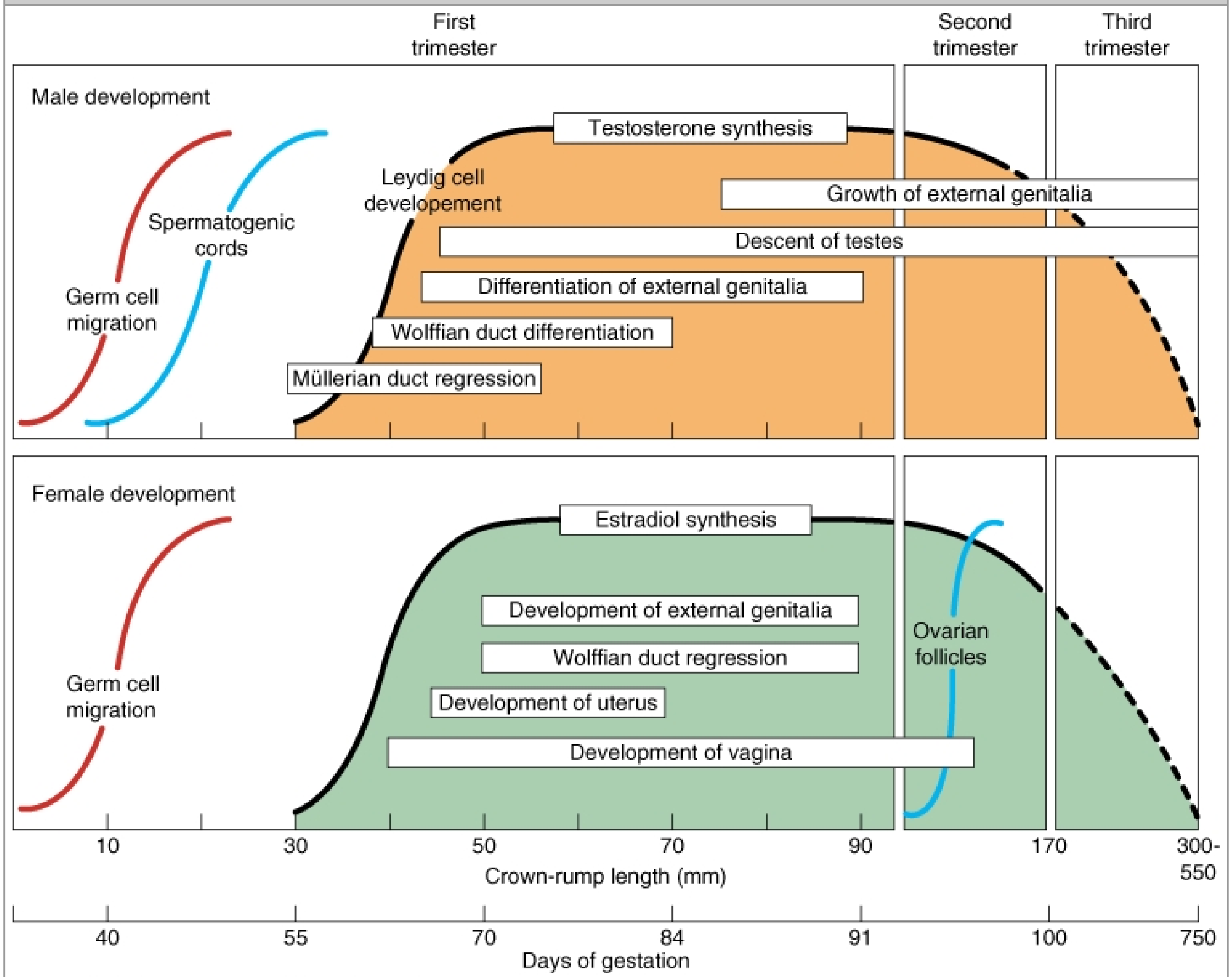
Development of the paramesonephric and mesonephric ducts in the male and female embryo. *(From Larsen, 2001, with permission.)*

The developing Sertoli cells begin to secrete mÃ¼llerian-inhibiting substance (MIS) during weeks 7 to 8 of development. This gonadal hormone causes regression of the ipsilateral paramesonephric (mÃ¼llerian duct) system and this involution is completed by 9 to 10 weeks' gestation (Marshall, 1978). MÃ¼llerian-inhibiting substance may also control the rapid gubernacular growth necessary for the transabdominal descent of the testis. Serum MIS levels remain elevated in boys during childhood and then decline at puberty to the low levels seen in adult men. In contrast, girls have undetectable levels of MIS until the onset of puberty when serum MIS levels become measurable. The clinical significance of MIS, however, in pubertal and adult women is unknown.

In the testes, Leydig cells arise from the original mesenchyme of the gonadal ridge and lie between the testicular cords. Their differentiation begins approximately 1 week after Sertoli cell development. The Leydig cells begin to secrete testosterone by 8 weeks' gestation, and testosterone production peaks at weeks 15 to 18 as a result of stimulation of the testes by human chorionic gonadotropin (hCG). Testosterone acts in a paracrine manner on the ipsilateral mesonephric (wolffian) duct to promote virilization of the duct into the epididymis, vas deferens, and seminal vesicle. The androgens testosterone and dihydrotestosterone (the 5α reduced metabolite of testosterone, formed peripherally in the genital skin) are essential for the development of the male phenotype. These androgens control the differentiation and growth of the internal and external genitalia and also prime male differentiation of the brain.

In the female embryo, without the influence of the SRY gene, the bipotential gonad develops into an ovary. This development follows that of the testes by about 2 weeks and is characterized by the absence of testicular cords in the gonad. Ovarian determinant genes, although likely playing an active role in gonadal morphogenesis, are required only at later stages of development (Taylor, 2000). The primitive sex cords degenerate and the mesothelium of the genital ridge forms secondary sex cords (see Fig. 18-2). These secondary sex cords become the granulosa cells and the follicular structures that surround the germ cells. The medullary portion of the gonad regresses and forms the rete ovarii within the ovarian hilum. The primordial germ cells proliferate by mitosis and reach a peak number of 5 to 7 million by 20 weeks' gestation. At this time, the fetal ovary demonstrates mature organization with the presence of stroma and primordial follicles containing oocytes. The oocytes begin meiosis and arrest at the diplotene phase of meiosis I until the oocyte undergoes ovulation after menarche. Atresia of the oocytes starts in utero, leading to a reduced number of germ cells at birth (Fig. 14-1). A scheme of prenatal reproductive system development is presented in Fig. 18-3.

FIGURE 18-3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Development of the reproductive system. *(From Wilson, 1981, with permission.)*

Ductal System Development

Sexual differentiation of the reproductive ducts begins early in the fetal period and is attributed to the influence of gonadal hormones (testosterone and MIS) on the mesonephric (wolffian) and paramesonephric (mÃ¼llerian) ducts.

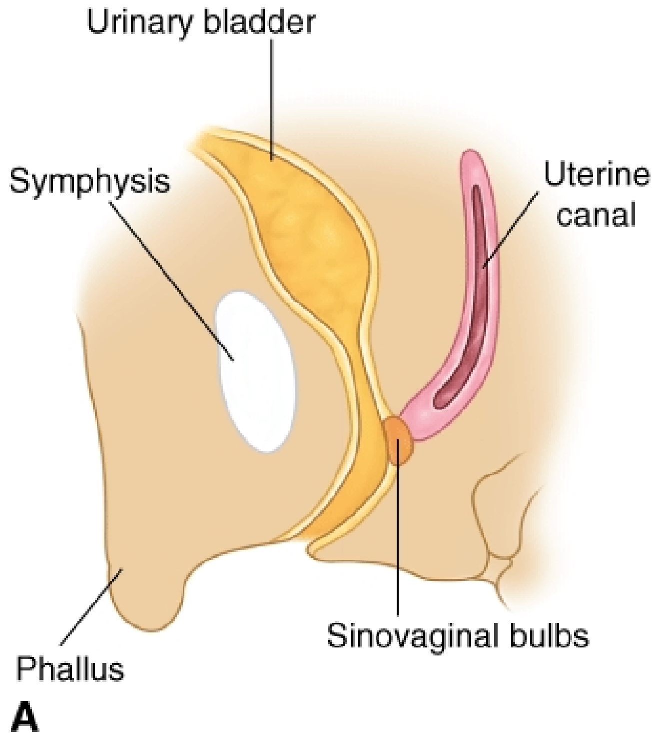
In the female, in the absence of MIS, the mÃ¼llerian ducts persist. These ducts grow caudally and along with the mesonephric ducts become enclosed in peritoneal folds that later give rise to the broad ligaments of the uterus. At about 10 weeks' gestation, the two distal portions of the mÃ¼llerian ducts approach each other in the midline and begin to fuse even before they reach the urogenital sinus. The fused ducts form a tube with a single lumen called the uterovaginal canal, which then inserts into the urogenital sinus at MÃ¼ller tubercle (Fig. 18-1E). This canal forms the uterus and upper portion of the vagina (Fig. 18-1F).

In a normal female, the uterine corpus and cervix differentiate, and the uterine wall thickens by 12 weeks' gestation. Initially, the upper pole of the uterus contains a thick midline septum that undergoes dissolution to create the uterine cavity. Dissolution of the uterine septum is usually completed by 20 weeks. The unfused cephalad portions of the mÃ¼llerian ducts become the fallopian tubes (Fig. 18-1F). Any failure of lateral fusion of the two mÃ¼llerian ducts or failure to reabsorb the septum between them results in separate uterine horns or some degree of persistent midline uterine septum. Moreover, vaginal agenesis is caused by failed

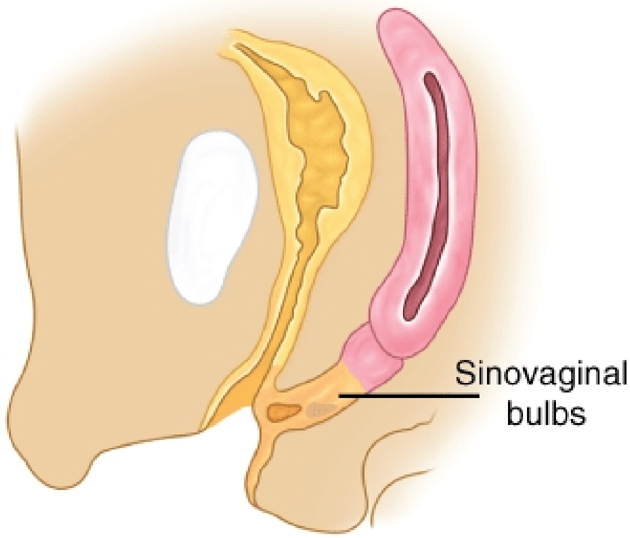
caudal migration of these ducts.

The distal third of the vagina develops from the bilateral sinovaginal bulbs, which arise from the urogenital sinus (Fig. 18-4A). The most inferior portion of the uterovaginal canal becomes occluded by a cellular mass derived from the sinovaginal bulbs, termed the vaginal plate (Fig. 18-4B). The cells of the vaginal plate desquamate during the second trimester, allowing for full canalization of the vaginal lumen (Fig. 18-4C). Defects in vertical fusion caused by incomplete canalization of this plate can lead to a persistent transverse vaginal septum. Septa can develop at varying levels within the vagina and be of various thicknesses (Fig. 18-5).

FIGURE 18-4

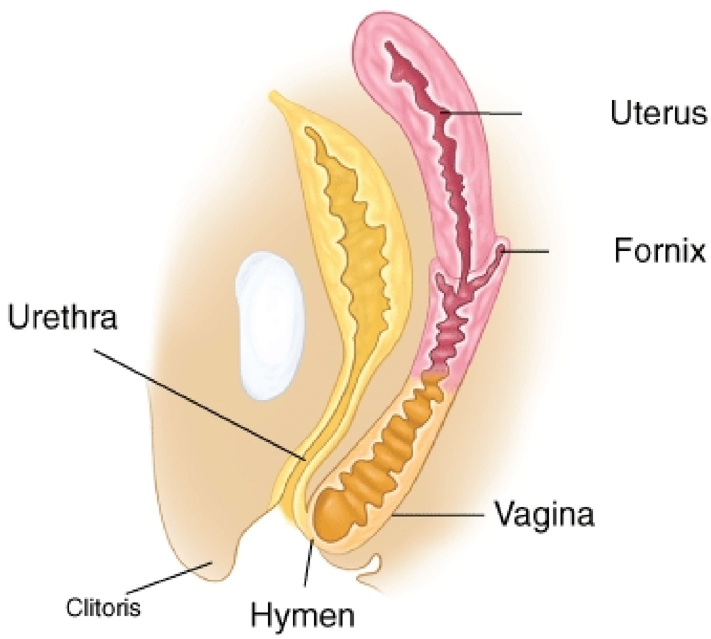


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

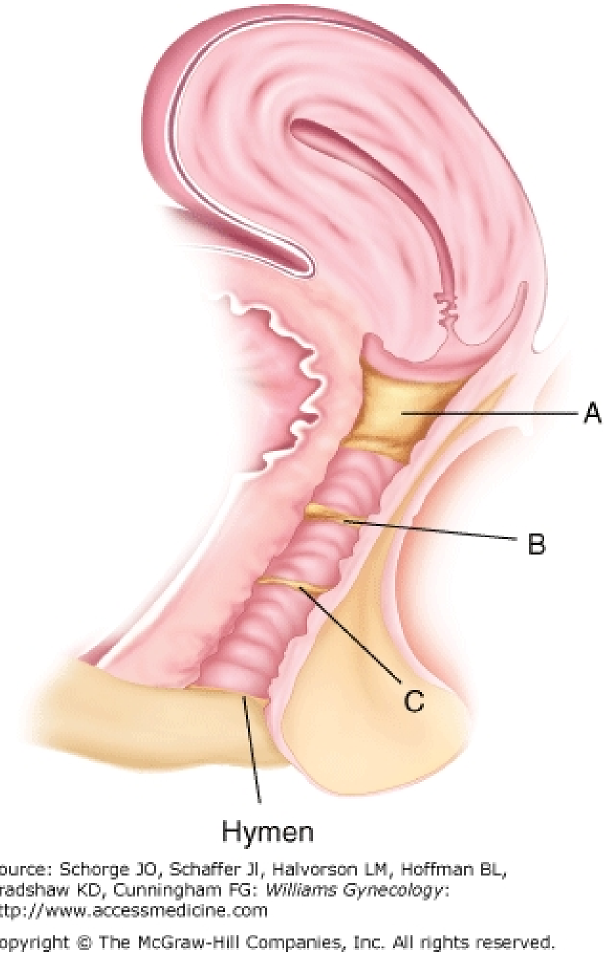


C

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Development of the uterus and vagina. **A.** Nine weeks. **B.** End of third month. **C.** Newborn. *(From Sadler, 2000, with permission.)*

FIGURE 18-5



Potential locations of a transverse vaginal septum are noted by **A, B** , and **C.** An imperforate hymen is also shown. *(From Rock, 1982, with permission.)*

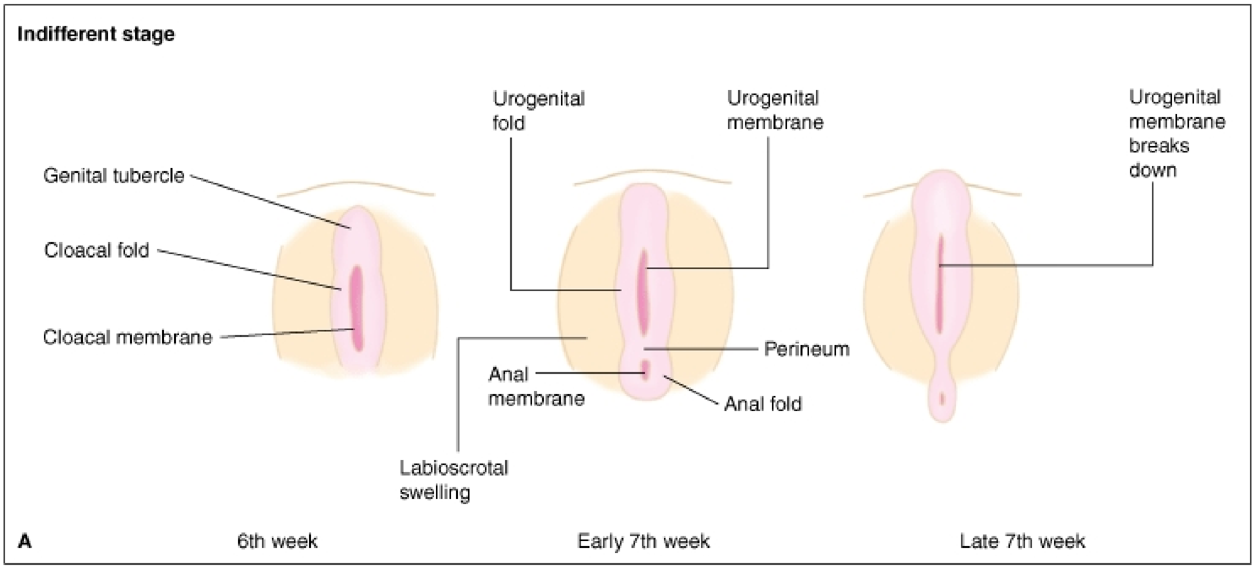
The hymen is the partition that remains to a varying degree between the dilated, canalized, fused sinovaginal bulbs and the urogenital sinus. The hymen usually becomes perforated shortly before or after birth. An imperforate hymen represents persistence of this membrane (Fig. 18-4C).

Although in each sex the ducts marked for degeneration do regress, vestigial remnants can be found and may become clinically apparent. In females, mesonephric remnants may give rise to structures such as Gartner duct cysts and to tubular epoÃ¶phoron and paroÃ¶phoron found in the mesoovarium (see Fig. 18-2). In males, a small vestige of the paramesonephros called the appendix testis may be identified.

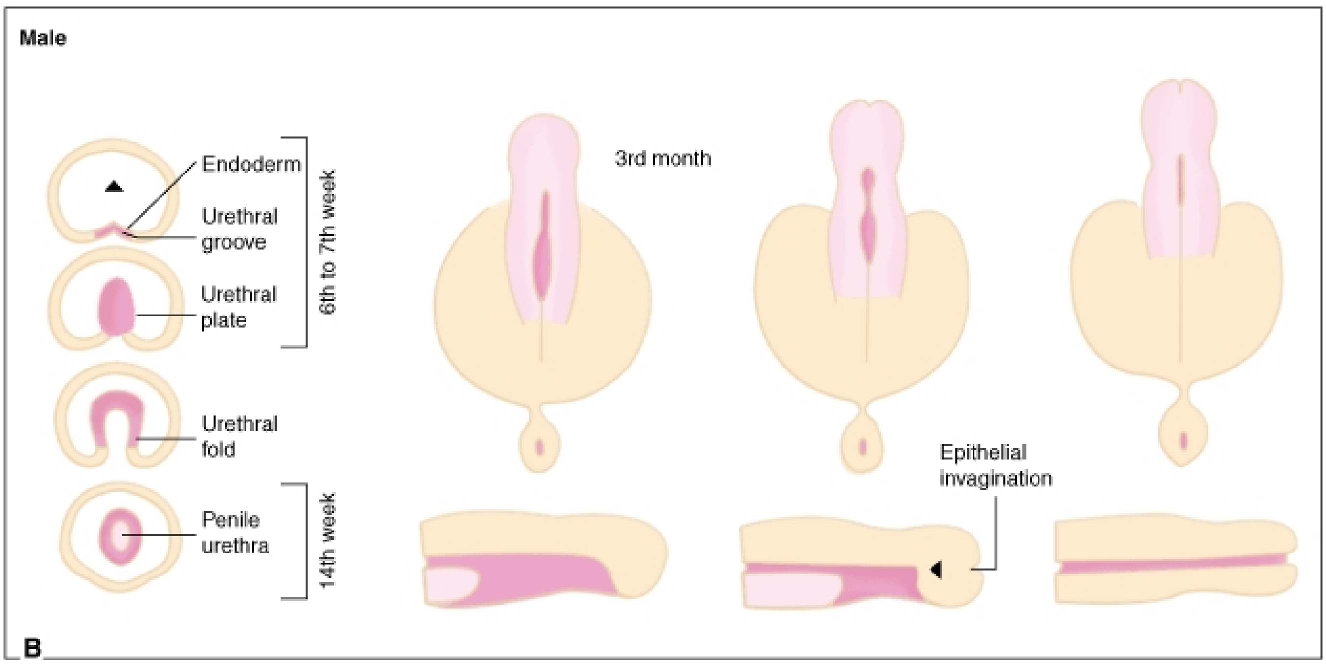
External Genitalia

Early development of the external genitalia is similar in both sexes. By 6 weeks' gestation, three external protuberances have developed surrounding the cloacal membrane. These are the left and right genital swellings, which meet ventrally to form the third protuberance, the genital tubercle (Fig. 18-6A). Ultimately, the genital swellings become the labioscrotal folds. The urogenital sinus extends onto the surface of the enlarging genital tubercle to form the urethral groove, which is flanked on either side by the urethral folds and lies within the labioscrotal folds. By week 7 of gestation, the urogenital membrane ruptures exposing the cavity of the urogenital sinus to the amniotic fluid (Fig. 18-7). The genital tubercle elongates to form the phallus in males and the clitoris in females. The coronary sulci that surround the phallus represent the primordium of the glans penis and glans clitoris.

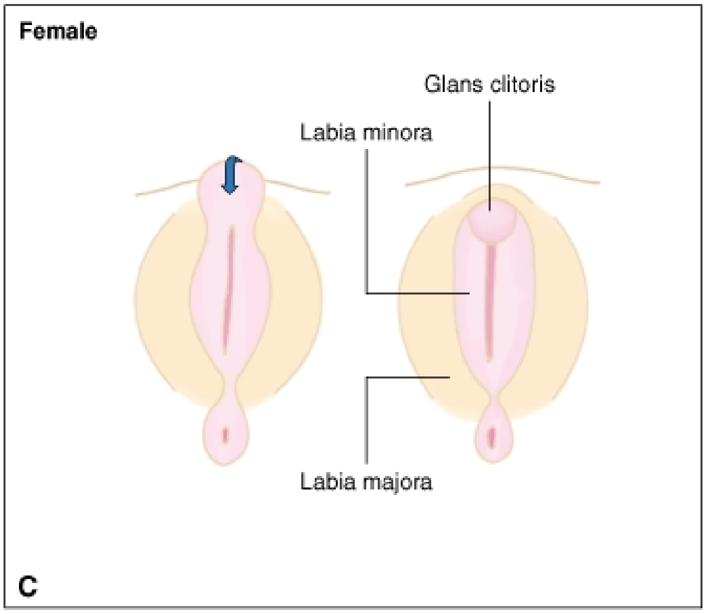
FIGURE 18-6



Indifferent stage
Urogenital fold
Urogenital membrane
Urogenital membrane breaks down
Genital tubercle
Cloacal fold
Cloacal membrane
Perineum
Anal membrane
Anal fold
Labioscrotal swelling
A
6th week
Early 7th week
Late 7th week



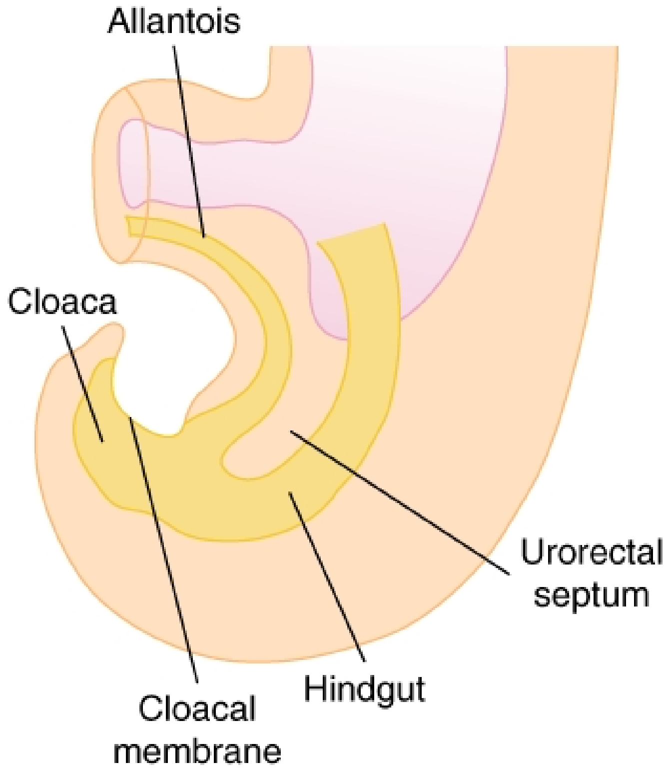
Male
Endoderm
Urethral groove
Urethral plate
6th to 7th week
3rd month
Urethral fold
Penile urethra
14th week
Epithelial invagination
B



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

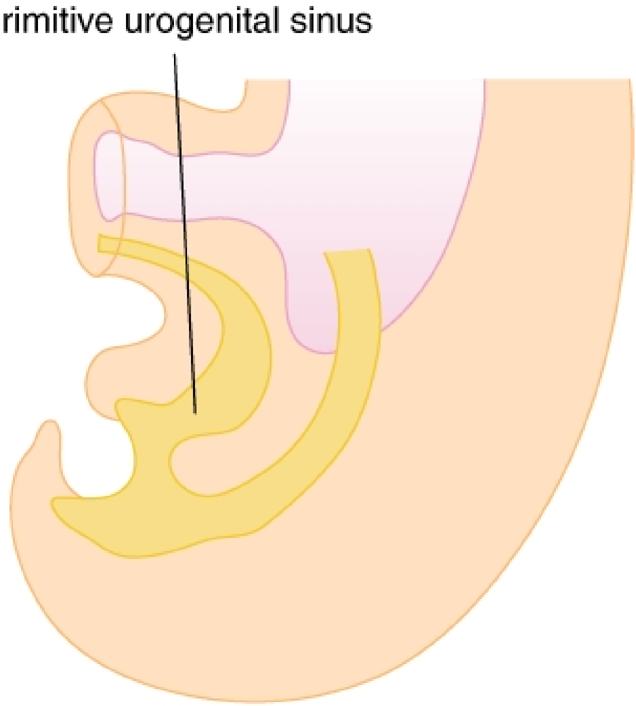
Development of the external genitalia. **A.** Indifferent stage. **B.** Virilization of external genitalia. **C.** Feminization. *(From Larsen, 2001, with permission.)*

FIGURE 18-7



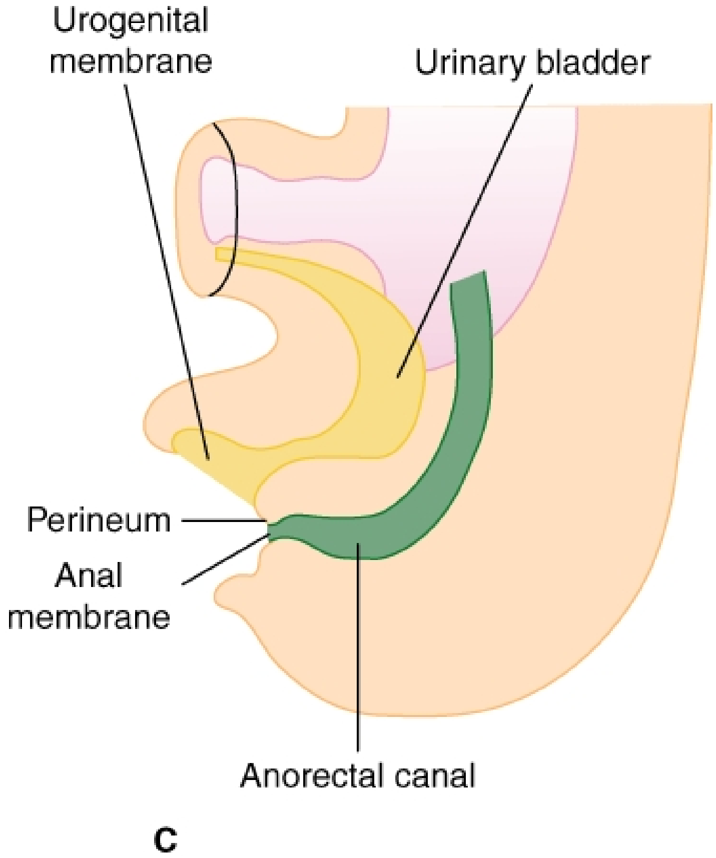
A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

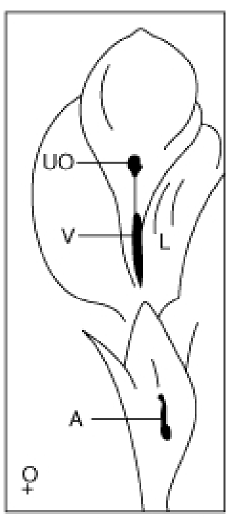
Development of the lower urinary and gastrointestinal tracts. (*From Sadler, 2000, with permission.*)

It is not until week 12 of gestation that one is able to visually identify a difference between male and female external genitalia (Fig. 18-8). In the male fetus, because of the effects of dihydrotestosterone (DHT) formed locally by the 5-α reduction of testosterone, the anogenital distance lengthens, the phallus enlarges, the labioscrotal folds fuse to form the scrotum, and subsequently the urethral folds merge to enclose the penile urethra (Fig. 18-6B). In the female fetus, in the absence of DHT, the anogenital distance does not lengthen, and the labioscrotal and urethral folds do not fuse (Fig. 18-6C). The genital tubercle bends caudally to become the clitoris and the urogenital sinus becomes the vestibule of the vagina. The labioscrotal folds become the labia majora, whereas the urethral folds persist as the labia minora (Gell, 2003).

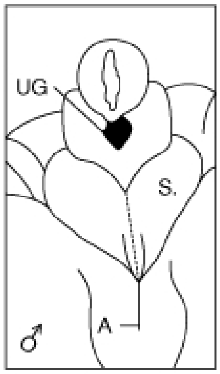
FIGURE 18-8

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Scanning electron micrographs of external genitalia. **A.** 11-week female fetus. **B.** 10-week male fetus. A = anus; L = labia majora; S = scrotal fold; UG = urethral groove; UO = urethral orifice; V = vagina. *(From O'Rahilly, 2001, with permission.)*

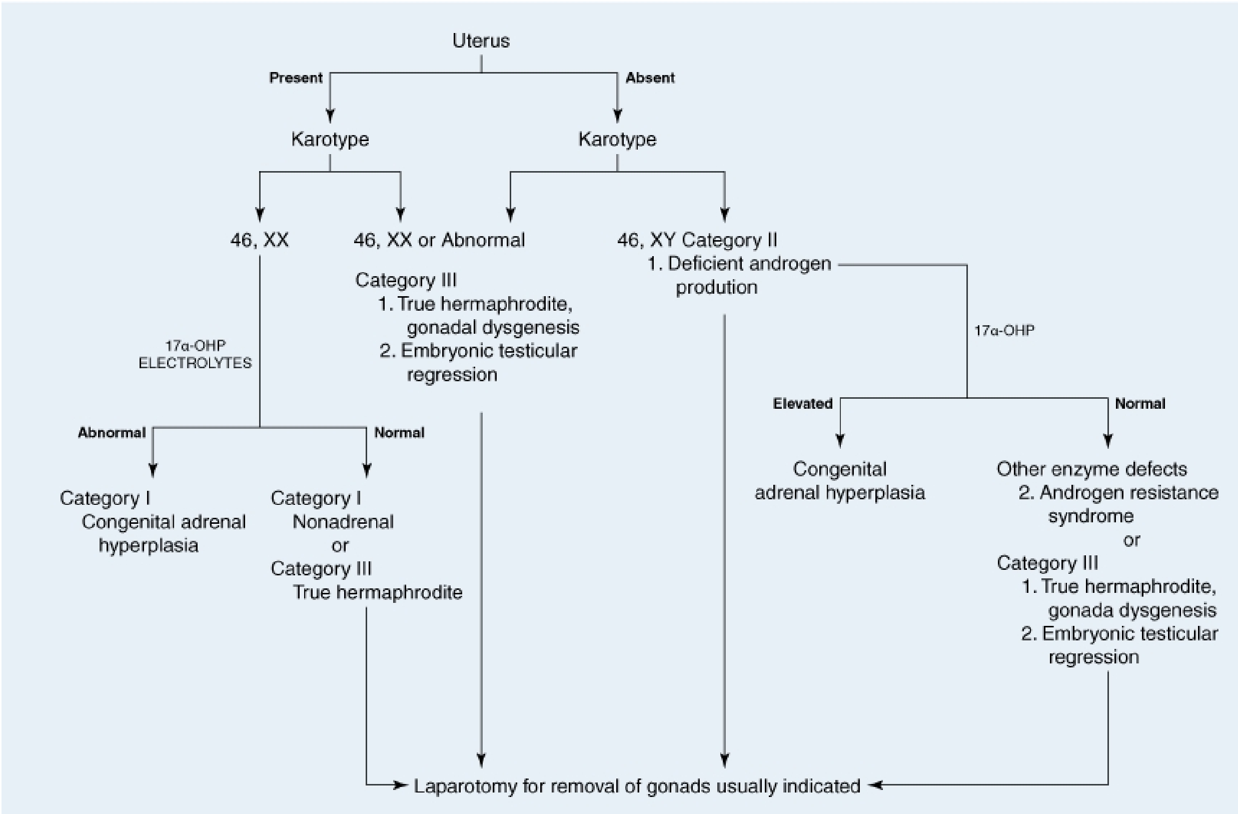
CONGENITAL AMBIGUITY OF THE GENITAL TRACT

Assignment of sex to the newborn at the time of birth usually involves a simple assessment of the external genitalia and a straightforward declaration of male or female gender. Ambiguous external genitalia in a newborn may pose a true medical emergency and present an important diagnostic challenge (Fig. 18-9). Genital ambiguity results from abnormal or inappropriate androgen exposure in utero. Table 18-1 presents a classification scheme for the evaluation of the newborn with sexual ambiguity.

Table 18-1 Classification of Ambiguous Genitalia

Category I	Female pseudohermaphroditism
Category II	Male pseudohermaphroditism
Category III	Disorders of genetic or gonadal development
	A. Gonadal dygenesis
	B. True hermaphroditism
	C. Embryonic testicular regression

FIGURE 18-9



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Evaluation of ambiguous genitalia. 17-OH-P = 17-hydroxyprogesterone. *(From Gant, 1993, with permission.)*

Female Pseudohermaphroditism (Category I)

PATHOPHYSIOLOGY

Discordance between gonadal sex (46,XX) and phenotypic appearance of the external genitalia (masculinized) results from excessive androgen exposure of an embryo or fetus. The ovaries and female internal ductal structures such as the uterus, cervix, and upper vagina are present. Accordingly, all patients with female pseudohermaphroditism are potentially fertile. The external genitalia, however, are virilized to a varying degree. This depends on the amount and the timing in embryonic development of androgen exposure. As a result, virilization may display an entire spectrum from modest clitoromegaly to development of a phallus with a penile urethra.

Excessive androgen exposure may stem from adrenal abnormalities or nonadrenal sources. Fetal congenital adrenal hyperplasia due to deficiency of 21-hydroxylase enzyme (CYP21) is the most common cause of female pseudohermaphroditism, with an incidence of approximately 1:14,000 live births (White, 2000). In addition, 11-β-hydroxylase (CYP11B) and 3β-hydroxysteroid dehydrogenase deficiency can also lead to ambiguous genitalia (see Fig. 15-13). Nonadrenal causes include maternal exposure to drugs such as testosterone, danazol, norethindrone, and other androgen derivatives. Maternal virilizing ovarian tumors, such as luteoma of pregnancy and Sertoli-Leydig cell tumor or virilizing adrenal tumors may be other sources. Fortunately, these neoplasms infrequently cause fetal virilization because of the tremendous ability of placental syncytiotrophoblasts to convert C_{19} steroids to estradiol (Cunningham, 2005).

TREATMENT

The three embryonic structures that are commonly affected by high androgen levels are the clitoris, labioscrotal folds, and urogenital sinus. Accordingly, a successful surgical correction must deal with all of these structural abnormalities to ensure a good cosmetic result and adequate sexual function. The objectives of feminizing genitoplasty are to: decrease the size of the enlarged clitoris while maintaining vascularity and sensory innervations; reduce and feminize the labioscrotal folds; and most importantly, address the urogenital sinus, which usually involves creating a separate vaginal introitus in the perineum (Hensle, 2002). Adequacy of the vagina for sexual intercourse is a major factor in these individuals if they desire fertility.

Male Pseudohermaphroditism (Category II)

PATHOPHYSIOLOGY

Insufficient androgen exposure of a fetus destined to be a male leads to male pseudohermaphroditism. The karyotype is 46,XY and testes are present. The uterus is generally absent as a result of normal embryonic MIS production. These patients are most often sterile from abnormal spermatogenesis and have a smaller or inadequate phallus for sexual function.

The etiology of male pseudohermaphroditism may involve: testicular enzyme defects in the biosynthesis of testosterone, peripheral enzyme defects, or abnormalities in the androgen receptor. Within the testes, there are five enzyme defects associated with impaired testosterone production. These include deficiencies of: (1) cholesterol side-chain cleavage enzyme (P450SCC); (2) 3β-hydroxysteroid dehydrogenase; (3) 17-α-hydroxylase; (4) 17, 20 desmolase (P450c17a); and (5) 17β-hydroxysteroid dehydrogenase. The latter two enzyme deficiencies can also cause congenital adrenal hyperplasia.

Peripherally, a defect in the enzyme 5α reductase leads to impaired conversion of testosterone to DHT, the active androgen in the peripheral tissue.

Finally, the androgen receptor may be defective and result in androgen-insensitivity syndrome (AIS). The gene for the androgen receptor is found on the long arm of the X chromosome. Mutations may result in the production of a nonfunctional receptor that will not bind androgen. Alternatively, mutations may lead to receptors that bind androgen but are unable to effect full transcriptional activation. The estimated incidence of AIS ranges from 1 in 13,000 to 41,000 live births (Bangsboll, 1992; Blackless, 2000).

PRESENTATION AND TREATMENT

As a result, there may be complete resistance, with no genital ambiguity (external genitalia appear as normal female), or an incomplete form associated with varying degrees of genital ambiguity. Milder forms of AIS have been described in men with infertility and poor virilization. Patients with complete androgen receptor insufficiency (CAIS), however, appear as phenotypically normal girls at birth and often present at puberty with primary amenorrhea. These girls develop breasts during pubertal maturation, but are found to have a blind-ending vagina and scant pubic and axillary hair. Laboratory evaluation demonstrates elevated LH levels, normal or slightly elevated male testosterone levels, and a 46,XY karyotype.

Treatment consists of replacement with physiologic levels of estrogen and creation of a functional vagina either by dilation or surgical vaginoplasty (Treatment). Additionally, surgical excision of the testes after puberty is recommended to decrease the associated risk of germ cell tumors in these individuals (see Chap. 36, Dysgerminoma). In adult life, those with CAIS have a female gender identity with a total inability to respond to androgens. Several reports suggest that these women have normal sexual function, but these reports were based on small sample sizes without using validated measures of sexual function (Lewis, 1986; Vague, 1983; Wisniewski, 2000). In contrast, Minto and colleagues (2003) evaluated 66 adult women with CAIS and found that 90 percent had some sexual difficulties compared with the general female population. Most commonly encountered problems included sexual infrequency and vaginal penetration difficulty.

Disorders of Genetic or Gonadal Development (Category III)

Several conditions, such as gonadal dysgenesis, true hermaphroditism, and embryonic testicular regression, may all lead to the development of ambiguous or infantile genitalia.

GONADAL DYSGENESIS

Gonadal dysgenesis results most often from nondisjunction of parental chromosomes and leads to abnormal gonadal development

and streak gonads. In 50 to 60 percent of patients with gonadal dysgenesis the karyotype is 45,X, and this condition is commonly called Turner syndrome. The classic stigmata of Turner syndrome include short stature (final height less than 58 inches), widely spaced nipples, and webbed neck. Additional physical findings are listed in Table 16-6. In these patients, associated problems may include cardiac anomalies (especially coarctation of the aorta), renal anomalies, hearing impairment, otitis media, and mastoiditis. They also carry an increased risk of hypertension, achlorhydria, diabetes mellitus, and Hashimoto thyroiditis. This syndrome may be recognized in childhood, but some patients are not diagnosed until adolescence, when they present with short stature, primary amenorrhea, hypergonadotropic hypogonadism, and prepubertal female genitalia. The uterus and vagina are normal and capable of responding to exogenous hormones.

Other patients with gonadal dysgenesis have a mosaic karyotype (e.g., 46,XX/45,X) or a structural abnormality of the second X chromosome. They may exhibit some or all of the stigmata of classic Turner syndrome. Patients with mosaicism are more likely to have some pubertal maturation. Gonadal failure is indicated by elevated gonadotropin levels.

Alternatively, the term *pure gonadal dysgenesis* includes patients with normal stature and gonadal abnormality of Turner syndrome. The karyotype may be 46,XX or 46,XY. The lack of a testis in XY patients results from the lack of testicular determining factors on the Y chromosome. As a result, streak gonads do not produce androgens or mÃ¼llerian inhibiting substance. This condition is also known as *Swyer syndrome* . The patients appear as normal prepubertal females including a normal mÃ¼llerian system. Because of a Y chromosome is present, these patients are at increased risk of gonadal tumors and thus require removal of the gonads.

TRUE HERMAPHRODITISM

A true hermaphrodite has both ovarian and testicular gonadal tissue. The most common karyotype associated with true hermaphroditism is 46,XX, followed by 46,XX/46,XY. The phenotype of a 46,XX true hermaphrodite includes a unilateral ovotestis with a contralateral ovary or testis, or bilateral ovotestes. The gonadal location varies from abdominal to inguinal to scrotal. The nature of the internal ductal system depends on the ipsilateral gonad and its degree of differentiation. The testicular products, MIS and testosterone, determine to what degree the internal ductal systems are masculinized or feminized. External genitalia are usually ambiguous and usually are undermasculinized due to an inadequate amount of testosterone.

In 46,XX sex-reversed males, male sexual differentiation occurs in the presence of a 46,XX karyotype. In this condition, varying lengths of DNA from the Y chromosome are translocated to the X chromosome during meiosis. The SRY gene is abnormally translocated to the X chromosome in about 60 percent of 46,XX sex-reversed males (Kolon, 1998; Schweikert, 1982). In individuals without translocated SRY, it is likely that downstream Y, X, or autosomal testicular determining factor genes are present or activated.

The presence of SRY guides the gonad to develop along testicular lines, and testicular hormone function is near normal. The mÃ¼llerian system regresses due to the production of MIS. Androgen production allows development of the wolffian system and masculinization of the external genitalia. Spermatogenesis, however, is absent due to absence of certain genes on the long arm of the Y chromosome. These individuals are not usually diagnosed until puberty or during an evaluation for infertility. The testes are usually small and may be cryptorchid. The penis may be small, and hypospadias is present in about 10 percent. Semen analysis reveals azoospermia due to absent spermatogenesis.

EMBRYONIC TESTICULAR REGRESSION

Lastly, embryonic testicular regression or agonadism may occur in a 46,XY individual. In these settings, MIS may or may not be produced, and therefore the uterus may be present or absent. Similarly, the karyotype may or may not be abnormal, that is, 46,XY/45X (mixed gonadal dysgenesis); 46,XX (true hermaphroditism); or 46,XY (embryonic testicular regression). There is variable androgen secretion among these disorders and thus phenotypic presentations may be diverse.

DEFECTS OF THE BLADDER AND PERINEUM

Description and Patient Presentation

Bladder exstrophy is thought to be caused by failure of the cloacal membrane to be reinforced by an ingrowth of mesoderm. The bilaminar cloacal membrane lies at the caudal end of the germinal disc and forms the infraumbilical abdominal wall. The normal ingrowth of mesoderm between the ectodermal and endodermal layers of the cloacal membrane leads to formation of the lower abdominal musculature and the pelvic bones. The cloacal membrane may prematurely rupture. Depending on the extent of the infraumbilical defect and the stage of development at which it ruptures, bladder exstrophy, cloacal exstrophy, or epispadias results (Gearhart, 1992).

The incidence of bladder exstrophy has been estimated to be between 1 in 10,000 and 1 in 50,000 (Lattimer, 1966; Rickham, 1960). This anomaly displays a predilection for males and the male:female gender ratio derived from multiple series approximates 2:1. Additional evidence for a genetic mode of transmission was noted by Shapiro and co-workers (1985). They determined that the risk of bladder exstrophy in the offspring of individuals with bladder exstrophy and epispadias is 1 in 70 live births, a 500-fold greater incidence than in the general population.

All cases of exstrophy have the characteristic widening of the symphysis pubis caused by the outward rotation of the innominate bones. This rotation accounts for the increased distance between the hips in these individuals and their associated waddling gait. In addition, Stanton (1974) noted that 43 percent of 70 females with bladder exstrophy also had associated reproductive tract anomalies. The urethra and vagina are typically short and the vaginal orifice is frequently stenotic and displaced anteriorly. The clitoris is duplicated or bifid, and the labia, mons pubis, and clitoris are divergent. The uterus, fallopian tubes, and ovaries are typically normal except for occasional mÃ¼llerian duct fusion defects.

Treatment

Reconstruction of the female genitalia presents a less complex problem than that of the male. Surgical functional closure is currently performed in the first 3 years of life as a staged surgical procedure. Generally, the bladder is closed first, followed by bladder neck reconstruction, and subsequent epispadias repair. Approximation of the clitoral halves in the sparsely hair-bearing skin of the mons pubis provides satisfactory cosmetic restoration (Damario, 1994; Dees, 1949). Vaginal dilatation or vaginoplasty may be required to allow satisfactory intercourse in the mature female (Jones, 1973). Long term, the defective pelvic floor may predispose women to uterine prolapse, making uterine suspension necessary (Gearhart, 1992).

DEFECTS OF THE CLITORIS

Clitoral Anomalies

Congenital abnormalities of the clitoris are unusual, but include clitoral duplication as well as excess androgen exposure leading to clitoral enlargement. Clitoral duplication, also known as *bifid clitoris* , usually develops in association with exstrophy or epispadias. The disorder is rare, with an incidence of 1 in 480,000 females (Elder, 1992).

The clitoris may also be affected by epispadias. In those with epispadias but without bladder extrophy, visibly apparent anomalies include a widened, patulous urethra; absent or bifid clitoris; nonfused labial folds (majora and minora); and flattened mons pubis. Female epispadias can be divided into three typesâ€” vestibular, subsymphyseal, and retrosymphysealâ€"which are differentiated by the type of urethral involvement (Schey, 1980). The vestibular type is an abnormality affecting only the distal urethra. The subsymphyseal type has a urethral abnormality present from its midportion (just beneath the symphysis) and extending distally. The retrosymphyseal designation describes an abnormality beginning at the proximal urethra and extending to the bladder neck. The most distal defect (vestibular type) is generally only an anatomic abnormality. In contrast, the likelihood of associated functional loss of sphincter control and incontinence increases considerably if the abnormality begins more proximally. The correlation of abnormal sphincter function with the degree of urethral abnormality is not absolute, however. Occasionally, patients with a mild form may be continent, but some degree of chronic wetness is common.

Most female patients with epispadias also have other serious physical disabilities. Incontinence causes perineal skin erosion and uriniferous odor. Vertebral abnormalities and diastases of the pubic symphysis are also commonly associated.

Mild degrees of abnormality, not associated with incontinence, may require only vulvoplasty. Those anomalies of the urethra or bladder or both associated with any degree of incontinence, however, need surgical correction. For this purpose, urethroplasty as well as Burch and Marshall-Marchetti-Kranz colposuspension procedures have all been employed. Correction of this anomaly is usually successful. Vesicoureteral reflux, if persistent after correction, however, requires ureteral reimplantation.

Another clitoral anomaly is the female phallic urethra and is found in association with a persistent cloaca (Sotolongo, 1983). The phallic urethra opens at the tip of the clitoris. This anomaly affects 4 to 8 percent of girls with persistent cloaca and has been described in association with embryonic exposure to cocaine (Karlin, 1989).

Clitoromegaly

Finally, clitoromegaly noted at birth is suggestive of fetal exposure to excessive androgens. Clitoromegaly is defined as a clitoral index greater than 10 mm^2 . Clitoral index is determined by the glans length times the width. Early androgen exposure leads to fusion of the labioscrotal folds and findings of a single perineal opening, the urogenital sinus. The labia display a rugated, scrotum-like appearance. A gonad in the groin or labia majora, however, should raise the concern of male pseudohermaphroditism.

In premature neonates, the clitoris may appear large normally, but it does not change in size and appears to regress as the infant grows. Other causes of clitoromegaly include breech presentation with vulvar swelling, chronic severe vulvovaginitis, and neurofibromatosis (Dershwitz, 1984; Greer, 1981).

Adult women with exposure to androgen excess may also present with some degree of clitoromegaly. The normal adult clitoris is generally 1 to 1.5 cm long and 0.5 cm wide in the nonerect state. Virilization of the female from excess levels of androgen may result in a variety of physical changes including not only clitoral enlargement, but also hirsutism, acne, oily skin, deepening of the voice, temporal balding, increase in muscle mass, and decrease in breast size.

LABIAL FUSION

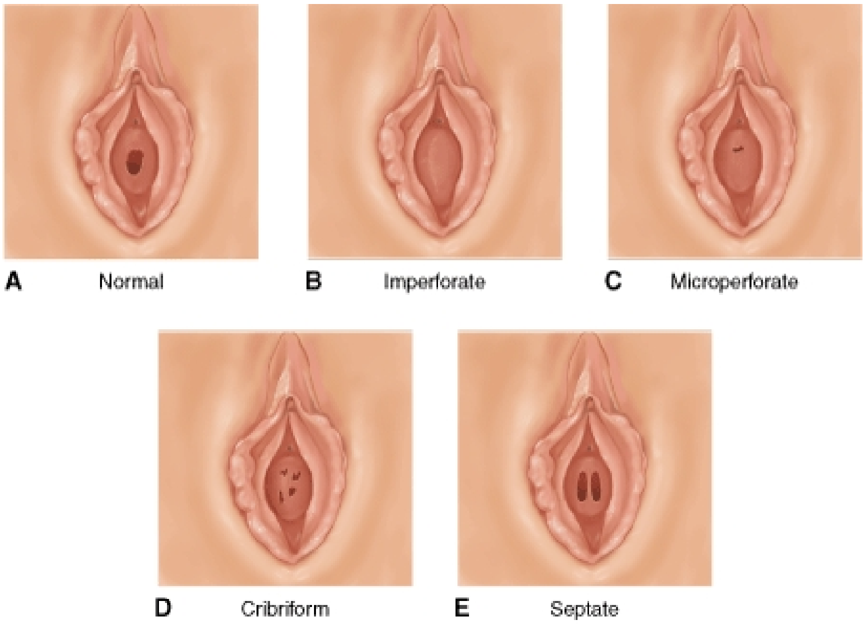
Fusion of the labia majora is a commonly acquired defect of the labia. It is typically found in young neonates or prepubertal girls when the labia and vagina are not adequately estrogenized. This fusion can range from a thin filmy adhesion to a dense scar and is discussed more fully in Chapter 14, Labial Adhesion (Reynolds, 1998).

HYMENEAL DEFECTS

Description and Patient Presentation

The hymen is the membranous vestige of the junction between the sinovaginal bulbs and the urogenital sinus (see Fig. 18-4C). It generally becomes perforate or patent during fetal life to establish a connection between the vaginal lumen and the perineum. A variety of hymeneal abnormalities may exist as shown in Figure 18-10, such as microperforate, septate, cribriform, and imperforate hymen (Breech, 1999). Imperforate hymen is due to complete failure of the inferior end of the vaginal plate to canalize and is noted in approximately 1 in 2,000 females (Parazzini, 1990). Although most cases occur sporadically, cases of imperforate hymen involving multiple family members have been reported (Lim, 2003; Stelling 2000; Usta, 1993).

FIGURE 18-10



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

F

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Types of hymens. **A.** Normal. **B.** Imperforate. **C.** Microperforate. **D.** Cribriform. **E.** Septate. **F.** Photograph of imperforate hymen. *(Courtesy of Dr. Ellen Wilson.)*

If the hymen is imperforate, mucus and blood from endometrial sloughing accumulate in the vagina. In infants, the obstructed vagina may distend from mucus accumulation, a condition termed *hydromucocolpos* . More commonly, however, adolescents present after menarche and menstrual blood trapped in the vagina behind the imperforate hymenâ€"*hematocolpos* â€"may create a bluish bulge at the introitus. With cyclic menstruation, the vaginal canal becomes greatly distended, and the cervix may begin to dilate and allow formation of a hematometra and hematosalpinx. Cyclic pain, amenorrhea, abdominal pain mimicking acute abdomen, and difficulty with urination or defecation may be present (Bakos, 1999). Retrograde menstruation may lead to the development of endometriosis. Other obstructive reproductive tract anomalies that are located more cephalad, such as transverse vaginal septum, may present similarly. The associated vulvar distension, however, uniquely suggests imperforate hymen.

Treatment of Hymenal Defects

Patients with microperforate, cribiform, or septate hymen will typically present with menstrual irregularities or with difficulty in tampon placement or intercourse. Repair of imperforate or microperforate hymen may be accomplished at essentially any time the diagnosis is made and is illustrated in Section 41-5, Hymenectomy. Breech and Laufer (1999) advocate repair when the tissues are under the influence of estrogen stimulation, either in infancy or after thelarche, but before menarche. This timing avoids the formation of hematocolpos and hematometra. Laparoscopy can be performed at the time of excision of an imperforate hymen to determine the presence of endometriosis. Clinicians should avoid needle aspiration of a hematocolpos for diagnosis or treatment. This may seed the retained blood with bacteria and place a patient at risk of infection. Moreover, recurrent hematocolpos secondary to inadequate drainage is common following needle aspiration alone.

Hymeneal cysts must be differentiated from an imperforate hymen with hydrocolopos (Nazir, 2006). These cysts typically have an opening and may regress spontaneously. They may also be treated by incision and drainage. Simple puncture has also been successfully performed.

TRANSVERSE VAGINAL SEPTUM

Description and Patient Presentation

Vertical fusion refers to complete cavitation of the vaginal plate between the sinovaginal bulbs and uterovaginal canal. Transverse vaginal septum may be caused by a failure of this process (see Fig. 18-5). The anomaly is uncommon, and Banerjee (1998) reported an incidence of 1 in 70,000 females. The septum may be obstructive, with accumulation of mucus or menstrual blood, or may be non-obstructive, allowing for egress of mucus and blood.

Transverse vaginal septum can develop at any level within the vagina but is more common in the upper portion, that is, at the junction between the sinovaginal plate and the caudal end of the fused mÃ¼llerian ducts (see Fig. 18-4). In a series reported by Rock (1982), 46 percent of septa were located in the upper vagina, 35 percent in the middle, and 19 percent in the lower portion of the vagina. The thickness of the septum may be variable, and thicker septa tend to be located nearer the cervix. Typically, a septum is thin (average thickness of 1 cm), but Rock (1982) reported septal thicknesses of 5 to 6 cm.

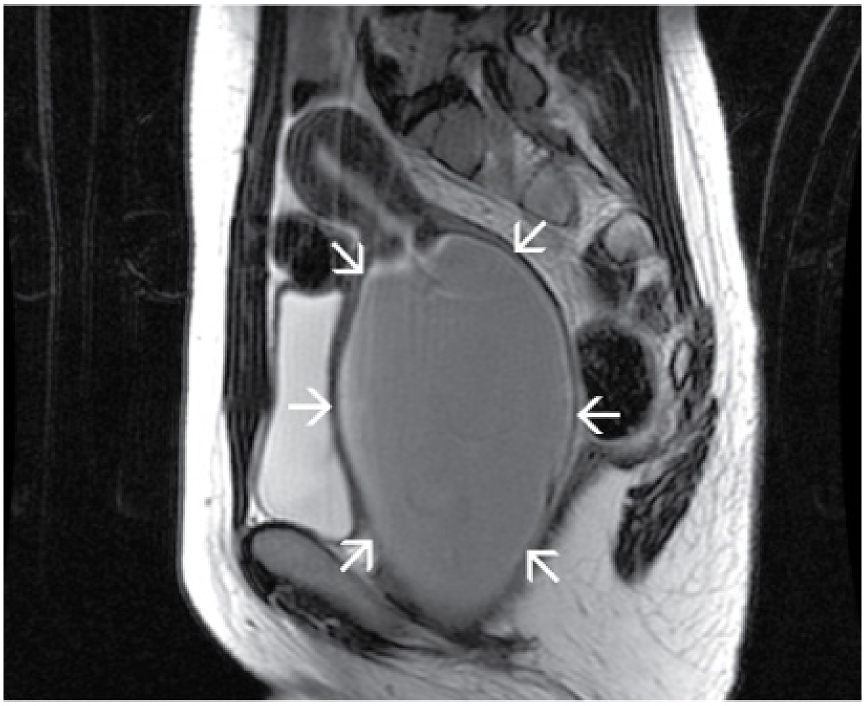
In neonates and infants, obstructive transverse vaginal septum has been associated with fluid and mucus collection in the upper vagina, resulting in a mass that that may be large enough to compress abdominal or pelvic organs (Adaletli, 2007). It has been reported to limit diaphragmatic movement, and neonatal deaths have been reported. In addition, pyomucocolopos, pyometria, and pyosalpinges may develop from ascension of vaginal or perineal bacteria through small perforations within the septum (Breech, 1999). In contrast to other defects of the mÃ¼llerian ducts, transverse vaginal septum is fortunately associated with few urologic abnormalities.

Patients with obstructive transverse vaginal septum usually present during adolescence with cyclic lower abdominal pain, amenorrhea, and gradual development of a central pelvic mass. Those with nonobstructive transverse vaginal septum will typically complain of abnormal menstrual flow, pain with intercourse, difficulty in placing or removing tampons, or obstructed labor.

Diagnosis and Treatment

The diagnosis is suspected when an abdominal or pelvic mass is palpated or when a foreshortened vagina and inability to identify the cervix is encountered. Diagnosis is confirmed by either sonography or magnetic resonance (MR) imaging. Magnetic resonance imaging is most helpful prior to surgery to determine the thickness and depth of the transverse septum (Fig. 18-11). In addition, MR imaging may identify if a cervix is present, thereby differentiating a high vaginal septum from cervical agenesis.

FIGURE 18-11



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Magnetic resonance image of complete low transverse septum with obstruction. Marked hematocolpos is identified (arrows) in this 13-year-old female. The relatively low signal intensity on T2-weighted imaging is consistent with subacute blood. The uterus is seen above the hematocolpos. *(Courtesy of Dr. Doug Sims.)*

Surgical repair is dependent upon septal thickness and skin grafts may occasionally be necessary to cover a defect left by excision of very thick septa. Smaller septa may be approached by excision with an end-to-end anastomosis of the upper to the lower vagina as described by Suidan (1979) (see Section 41-11, Transverse Vaginal Septum Excision). Sanfilippo (1986) recommends laparoscopy at the time of surgical therapy for transverse vaginal septum because of the high rate of endometriosis seen in association with outflow tract obstruction.

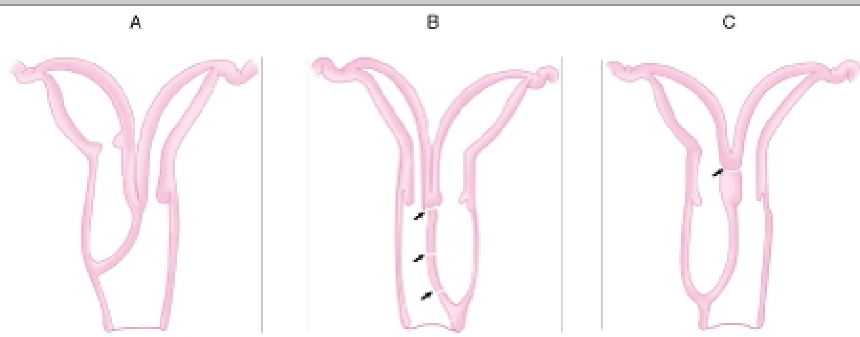
As an alternative to excision with end-to-end anastomosis, Garcia (1967) reported a Z-plasty technique that may minimize scar formation. Wierrani (2003) reported using Garcia's procedure in 13 patients. Postoperative scarring and resulting vaginal contracture did not develop. Postoperatively, patients were sexually active and reported satisfaction with sexual function.

LONGITUDINAL VAGINAL SEPTUM

A longitudinal vaginal septum results from defective lateral fusion and incomplete reabsorption of the paired mÃ¼llerian ducts. These septa are generally seen with partial or complete duplication of the cervix and uterus. Individuals complain of difficulty with intercourse or with complaints of vaginal bleeding despite tampon placement. The latter results from placement of the tampon into only one of the duplicated vaginas. The nonobstructed form can be managed conservatively unless dyspareunia develops. Surgical treatment includes resection of the longitudinal septum.

In addition, an obstructive variety of longitudinal vaginal septum can develop (Fig. 18-12). Typically the patient presents in adolescence with normal menarche, but reports worsening monthly unilateral vaginal and pelvic pain (Carlson, 1992). On examination, a patent vagina and cervix is noted, but a unilateral vaginal and pelvic mass can be seen. The mass represents obstruction of one of the hemivaginas associated with uterine duplication. Surgical correction consists of wide excision of the obstructing septum. Joki-Erkkila and Heinonen (2003) followed 26 females after surgical repair of obstructive outflow tract anomalies. They found a high rate of vaginal stricture requiring re-operation, as well as dysfunctional uterine bleeding, dyspareunia, and dysmenorrhea. Ipsilateral renal agenesis is extremely common with this malformation.

FIGURE 18-12



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Uterus didelphys with obstructed hemivagina. **A.** Complete obstruction. **B.** Partial vaginal communication. **C.** Partial uterine communication. *(From Rock, 1980, with permission.)*

GARTNER DUCT CYSTS

Gartner duct cysts are vestigial remnants of the wolffian ducts, and these mesonephric cysts are most commonly found on the cephalad, lateral wall of the vagina (see Fig. 18-2). The cysts are usually 1 to 5 cm in size and are typically found only incidentally during pelvic examination. A small asymptomatic Gartner duct cyst may be followed conservatively. Deppisch (1975) described 25 cases of symptomatic vaginal cysts. They reported a wide range of symptoms, including dyspareunia, vaginal pain, difficulty with tampon use, urinary symptoms, and palpable mass.

Symptomatic cysts may be treated by operative excision. Occasionally, these cysts may become infected, and if intervention is required during the acute phase, marsupialization of the cyst is preferred. Of note, excision of a vaginal cysts may be much more difficult and time consuming than anticipated, as some may extend up into the broad ligament and anatomically approximate the distal course of the ureter.

MÃ¼LLERIAN ANOMALIES

Incidence and Classification

Anomalies of the uterus may be congenital or acquired and typically present with abnormalities of the menstrual cycle, pelvic pain, infertility, or pregnancy wastage. The true incidence of congenital mÃ¼llerian anomalies, of which uterine malformations constitute the majority, is unknown. Most cases are diagnosed during evaluation for obstetric or gynecologic problems, but in the absence of

symptoms, most anomalies go undiagnosed. Because nearly 57 percent of women with uterine defects have successful fertility and pregnancy, the true incidence of congenital mÃ¼llerian defects may be significantly understated. Simon and colleagues (1991) found uterine anomalies in 3 percent of 679 fertile women undergoing laparoscopic tubal sterilization. Nahum (1998) found that the prevalence of uterine anomalies in the general population was 1 in 201 women or 0.5 percent.

Anatomic uterine defects have long been recognized as a cause of obstetric complications. Recurrent pregnancy loss, preterm labor, abnormal fetal presentation, and prematurity constitute the major reproductive problems encountered with developmental or acquired uterine malformations. MÃ¼llerian defects are also associated with renal anomalies in 30 to 50 percent of cases, ranging from renal agenesis and severe hypoplasia to ectopic or duplicate ureters (Sharara, 1998).

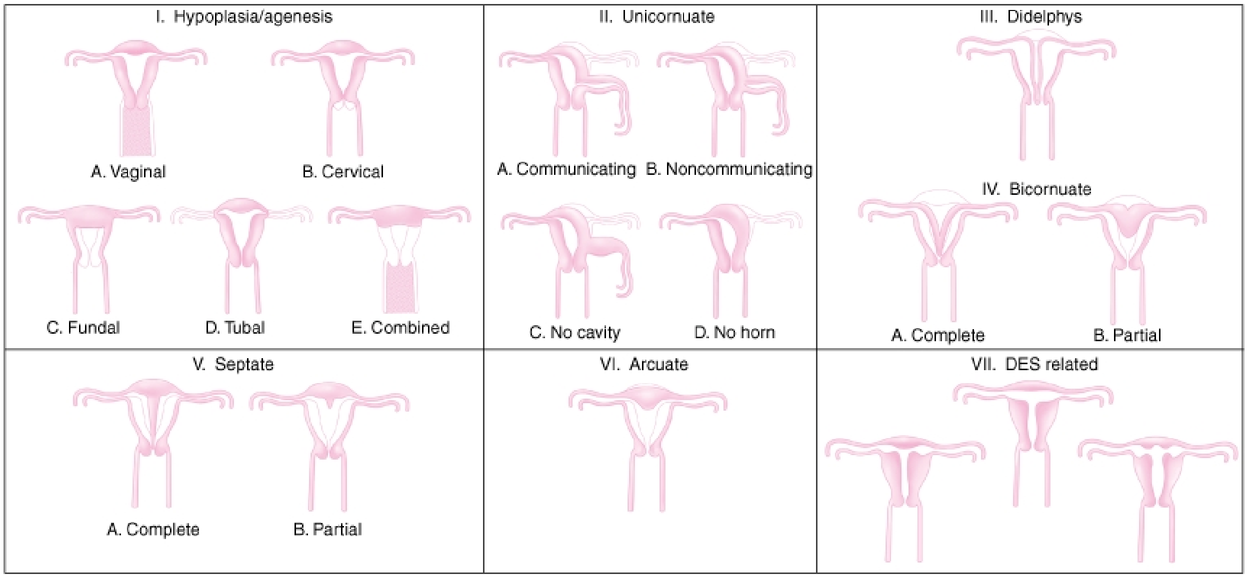
Congenital anomalies of the reproductive tract present a diagnostic challenge because of the variety of morphologic presentations. The apparent complexity can be greatly simplified by understanding the critical embryonic events that occur in normal mÃ¼llerian development. Various classification schemes for anomalies of the female reproductive tract exist, but the most common system was proposed by Buttram and Gibbons (1979) and adapted by the American Society of Reproductive Medicine (American Fertility Society, 1988) (Table 18-2). Within this system, six categories are used to classify similar embryonic developmental defects (Fig. 18-13).

Table 18-2 Classification of MÃ¼llerian Anomalies[a]
I. Segmental mÃ¼llerian hypoplasia or agenesis a. Vaginal b. Cervical c. Uterine d. Tubal e. Combined
II. Unicornuate uterus a. Rudimentary horn with cavity, communicating to unicornuate uterus b. Rudimentary horn with cavity, not communicating to unicornuate uterus c. Rudimentary horn with no cavity d. Unicornuate uterus without a rudimentary horn
III. Uterine didelphys
IV. Bicornuate uterus a. Complete bifurcation (bicollis) b. Partial bifurcation (unicollis)
V. Septate uterus a. Complete septation b. Partial septation
VI. Arcuate uterus
VII. Diethylstilbestrol-related anomalies

[a] See Figure 18-13 for drawings of these defects

From the American Society of Reproductive Medicine, 1988, with permission.

FIGURE 18-13



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Classification of mÃ¼llerian anomalies. DES = diethylstilbestrol. *(From American Society of Reproductive Medicine, 1988, with permission.)*

Segmental MÃ¼llerian Hypoplasia or Agenesis

PATHOPHYSIOLOGY AND PATIENT PRESENTATION

Some form of mÃ¼llerian hypoplasia or agenesis affects one in every 4,000 to 5,000 females and is a common cause of primary amenorrhea (Patton, 1994). Agenesis results from a defect in the development of the lower portion of the mÃ¼llerian ducts and usually leads to variable absence of the uterus, cervix, and/or upper part of the vagina (Fig. 18-13A).

VAGINAL AGENESIS

Females with vaginal atresia lack the lower portion of the vagina, but otherwise have normal external genitalia. The embryonic origin of this condition is presumed to involve failure of the urogenital sinus to contribute its expected caudal portion of the vagina (Simpson, 1999). As a result, the lower portion of the vagina, usually one fifth to one third of the total length, is replaced by 2 to 3 cm of fibrous tissue. In some individuals, however, vaginal atresia may extend to near the cervix.

Since most women with vaginal atresia have normal external genitalia and upper reproductive tract organs, this condition does not often become apparent until the time of expected menarche. Adolescents generally present shortly after physiologic menarche with cyclic pelvic pain due to hematocolpos or hematometra. On physical examination, normal breast and pubic hair development is present. The perineum is usually normal, with normal secondary sex characteristics with a hymeneal ring and beyond the ring, a vaginal dimple or small pouch. A rectoabdominal examination confirms the presence of midline structures. Additionally, sonographic or MR imaging will display upper reproductive tract organs. Of these, MR imaging is a more accurate diagnostic tool, as the length of the atresia, the amount of upper vaginal dilatation, and the presence or absence of a cervix can be identified. Laparoscopy, however, is necessary for diagnosis when the anatomy cannot be fully evaluated with radiographic studies. For example, Economy and associates (1998) reported that MR imaging has only 31-percent sensitivity for the detection of uterine structures in patients with vaginal agenesis. About one third of women with vaginal atresia have associated urologic abnormalities.

Vaginal atresia is distinct in clinical and embryonic characteristics from transverse vaginal septum. In patients with transverse vaginal septum there is a well-developed vagina in which a thick intervening septum separates the lower from the upper vagina. Conversely, in those with vaginal atresia, fibrous tissue develops in place of the vagina. In some, nearly the entire span beginning at the perineum and extending cephalad to the cervix may be fibrotic. Identification of the cervix in such cases distinguishes

vaginal atresia from mÃ¼llerian agenesis.

MÃ¼LLERIAN AGENESIS

A more common presentation of vaginal atresia is congenital absence of both the uterus and vagina, which is also referred to as *mÃ¼llerian aplasia* , *mÃ¼llerian agenesis* , or *Mayer-Rokitansky-KÃ¼ster-Hauser syndrome* . In classic mÃ¼llerian agenesis, patients have a shallow vaginal pouch, only measuring up to 1.5 inches deep. In addition, the uterus, cervix, and upper part of the vagina are absent. Typically, a portion of the distal fallopian tubes are present. In addition, normal ovaries are present, given their separate embryonic origin. Most patients with mÃ¼llerian agenesis have only small rudimentary mÃ¼llerian bulbs without endometrial activity. However, in 2 to 7 percent of women with this condition, active endometrium develops and patients typically present with cyclic abdominal pain (American College of Obstetricians and Gynecologists, 2002). Surgical excision of symptomatic rudimentary bulbs is required. With mÃ¼llerian agenesis, traditional conception is impossible, but pregnancy may be achieved using sophisticated technology involving oocyte retrieval, fertilization, and implantation into a surrogate. Evaluation for associated congenital renal or other skeletal anomalies is essential in individuals with mÃ¼llerian hypoplasia or agenesis. Approximately 15 percent of women with uterine agenesis also have defects of the urinary system, and 12 percent may have scoliosis.

TREATMENT

One treatment goal for most of these women is creation of a functional vagina. This may be accomplished conservatively or surgically. There are several conservative approaches, and each attempts to progressively invaginate the vaginal dimple to create a canal of adequate size. Graduated hard glass dilators were initially recommended by Frank (1938). Ingram (1981) modified the Frank method by affixing the dilators to a bicycle seat mounted upon a stool. This affords patients hand mobility for other activities during the 30 minutes to 2 hours spent each day for passive dilation (American College of Obstetricians and Gynecologists, 2002). Currently, firm silicon dilators are available through several medical vendors. A vagina may also be created with repeated coitus. Overall, vaginal dilatation techniques are successful in forming a functional vaginal in as many as 90 percent of cases (Croak, 2003; Roberts, 2001).

Surgical procedures are seen by many as a more immediate solution to creation of a neovagina, and several methods have been reported. The method used most commonly by gynecologists is the McIndoe vaginoplasty (McIndoe, 1950). As illustrated in Section 41-12, McIndoe Procedure, a canal is created within the connective tissue between the bladder and rectum. A split-thickness skin graft obtained from the patient's buttocks or thigh is then used to line the neovagina. Strickland (1993) reported excellent function and patient satisfaction.

Modifications of the McIndoe procedure include the use of human amnion, peritoneum, buccal mucosa, and Interceed absorbable adhesion barrier (Ethicon, Somerville, NJ) as neovaginal linings (Ashworth, 1986; Lin, 2003; Ozgenel, 2003; Motoyama, 2003). For example, Jackson and Rosenblatt (1994) described four cases of vaginoplasty using Interceed absorbable adhesion barrier. This method is less invasive than acquiring a skin graft, but complete epithelialization of the new vaginal wall requires 3 to 6 months. Noguchi and others (2004) reported the successful creation of a neovagina using artificial dermis (atelocollagen sponge) and the use of postoperative recombinant basic fibroblast growth factor spray to accelerate epithelialization. Squamous epithelialization of the vaginal epithelium was confirmed by histologic examination at 50 days after the operation, and no stenosis was observed.

Similarly, cutaneous or musculocutaneous flaps have been employed to line the neovagina. For example, the Williams vaginoplasty creates a vaginal pouch using labial skin flaps (Williams, 1964). This may not be as acceptable to young women, as it creates an awkward angle for sexual intercourse and a less cosmetically pleasing appearance.

All of these methods require a commitment to scheduled postoperative dilatation to avoid significant vaginal stricture (Breech, 1999). Accordingly, these procedures should be considered only if the patient is mature and willing to adhere to a postoperative regimen of regular intercourse or manual dilatation with dilators.

To avoid this necessity, pediatric surgeons more frequently use a segment of bowel to create the vagina. These colpoplasties most commonly use sigmoidal or ileal segments and require laparotomy and bowel anastomosis. Moreover, many patients complain of a persistent vaginal discharge from the gastrointestinal mucosa. In contrast, the Vecchietti procedure uses an initial abdominal surgery to place an apparatus for passive vaginal dilatation. The apparatus is a sphere and two guide wires. The sphere, attached

to the two wires, is placed in the vaginal dimple. The wires are guided through the potential neovaginal space to exit on the anterior abdominal wall. From the anterior abdominal wall, external pressure is exerted, which is increased daily to allow the blind vaginal pouch to be stretched by the sphere (Vecchietti, 1965).

Unicornuate Uterus

Arrested or defective development of only one of the mÃ¼llerian ducts results in a unicornuate uterus (Fig. 18-13B). The incidence of unicornuate uterus, as diagnosed by hysterosalpingography (HSG), in a series of 1,160 uterine anomalies was 14 percent (Zanetti, 1978). This was likely an underestimation, because HSG cannot be used to identify noncommunicating rudimentary horns, by far the most common anomaly.

Women with a unicornuate uterus have an increased incidence of infertility, endometriosis, and dysmenorrhea (Fedele, 1987; Heinonen, 1983). Reproductive performance of the unicornuate uterus is significantly impaired, and fetal survival rates are poor. Akar (2005) reported a live birth rate of only 29 percent in women with unicornuate uterus. A substantial percentage of these pregnancies, about 45 percent, are lost within the first two trimesters. Premature delivery is also a risk, occurring in 20 percent of all pregnancies in patients with this defect. Obstetric complications, such as breech presentation, fetal growth restriction, dysfunctional labor, and cesarean delivery are also more common (Acien, 1993).

The pathogenesis of pregnancy loss associated with unicornuate uterus is incompletely understood, but reduced uterine capacity that does not permit adequate gestational growth and development is a possible mechanism. In the unicornuate uterus, fetal growth restriction appears to be correlated with vascular anomalies in the distribution of the uterine artery (Burchell, 1978). These observations suggest that congenital alterations in blood flow mediate uterine and placental growth disturbances. Moreover, a relative cervical incompetence may contribute to the risk for premature delivery and late-trimester abortion. Accordingly, a unicornuate uterus should be suspected in any woman with a history of pregnancy loss, premature delivery, or abnormal fetal lie.

DIAGNOSIS AND MANAGEMENT

On physical examination, the uterus is often markedly deviated, reflecting the developmental failure of one of the mÃ¼llerian ducts. Hysterosalpingography, combined with sonography or MR imaging, is a key study in the evaluation. Typically, HSG films show a deviated banana-shaped cavity with a single fallopian tube. Rudimentary development of a uterine horn in association with a unicornuate uterus is best confirmed by sonography. This modality is sufficiently accurate and may be more reliable than laparoscopy in determining whether rudimentary structures are cavitary and thus contain endometrial tissue. Three-dimensional transvaginal sonography has also been used reliably in an office setting to diagnose and classify mÃ¼llerian anomalies (Raga, 1996).

Data from the combined series of 38 patients reported by Buttram and Gibbons (1979) and Fedele and associates (1987) indicate that approximately 65 percent of unicornuate uteri have an associated rudimentary horn. Thirty-one percent contained endometrial tissue, and one half of these communicated with the main uterine cavity. A rudimentary horn without an endometrial cavity was present in 34 percent of cases.

Pregnancies in the noncommunicating rudimentary horn are associated with a high rate of uterine rupture. These pregnancies are thought to occur by the intra-abdominal transit of sperm from the normal horn. Rolen and associates (1966) reported that uterine rupture occurred prior to 20 weeks in most of 70 rudimentary horn pregnancies. Nahum (2002) reviewed the literature from 1900 to 1999 and identified reports of 588 such pregnancies. In 419 cases, the communication status was known and half of these had uterine rupture, 80 percent before the third trimester. Eighty-five percent of the horns were of the noncommunicating type, and the rupture rate in these was 85 percent. Fetal survival was 6 percent overall in the 588 cases. More liberal use of sonography and MR imaging may result in an earlier diagnosis of cavitary rudimentary horns. Because of the high risk for maternal morbidity secondary to rupture with pregnancy and intraperitoneal hemorrhage, excision of a cavitary rudimentary horn is indicated whenever it is identified (Heinonen, 1997). To that end, Dicker (1998) reported the laparoscopic removal of rudimentary horn pregnancy. If the rudimentary horn is nonfunctioning (solid, with no functional endometrium) removal is not routinely recommended, as no adverse effect on reproductive outcome has been reported. Salpingectomy or salpingo-oophorectomy on the side with the rudimentary horn, however, has been suggested to prevent ectopic pregnancy in women with a unicornuate uterus, although in the series of Buttram, the ectopic pregnancy risk was low.

Uterine Didelphys

A didelphic uterus results when there is failed fusion of the paired mÃ¼llerian ducts (Fig. 18-13C). This anomaly is characterized by the presence of two endometrial cavities, each with a uterine cervix. A longitudinal vaginal septum runs between the two cervices in most cases. Heinonen (1984) reported that all 26 women with uterine didelphys in his series had a longitudinal vaginal septum. Occasionally, one hemivagina is obstructed by an oblique or transverse vaginal septum (Fig. 18-12A) (Hinckley, 2003).

Uterine didelphys should be suspected if a longitudinal vaginal septum or if two separate cervices are discovered. This anomaly may be identified during sonography (see Fig. 2-19). To confirm the diagnosis, HSG is recommended to identify the possibility of communication between the uteri (Fig. 19-7C).

Of all the major uterine malformations, the didelphic uterus has the best reproductive prognosis. Specifically, when compared with the unicornuate uterus, the potential for uterine growth and capacity appears similar. However, compared with a unicornuate uterus, uterine didelphys probably has an improved blood supply through collateral connections between the two horns. Alternatively, improved fetal survival may be secondary to earlier diagnosis of the uterine didelphys (because of the vaginal septum), which favors earlier and more intensive prenatal care (Patton, 1994). Heinonen (2000) surveilled 36 women with uterus didelphys. He found that 34 out of 36 women (94 percent) who wanted to conceive had at least one pregnancy, and they produced 71 pregnancies. Of these pregnancies, 21 percent were spontaneously aborted and 2 percent were ectopic. The rate for fetal survival was 75 percent; for prematurity, 24 percent; for fetal growth restriction, 11 percent; for perinatal mortality, 5 percent; and for cesarean delivery, 84 percent. Pregnancies located more commonly (76 percent) in the right uterus than in the left. Because the spontaneous abortion rate mirrors that of women with normal uterine cavities, surgical procedures in response to pregnancy loss are rarely indicated. Thus, surgery should be reserved for highly selected women in whom repeated late-trimester losses or premature delivery has occurred with no other apparent etiology.

Bicornuate Uterus

PATHOPHYSIOLOGY AND REPRODUCTIVE OUTCOME

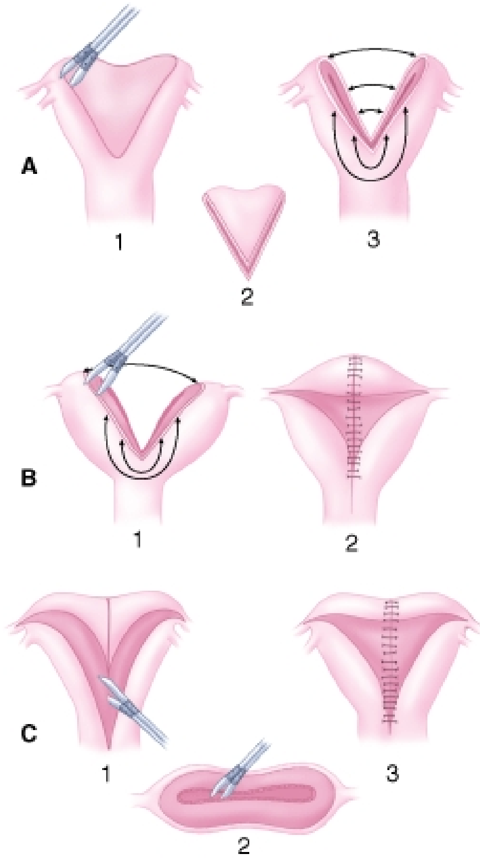
A bicornuate uterus is caused by incomplete lateral fusion of the mÃ¼llerian ducts. It is characterized by two separate but communicating endometrial cavities and a single uterine cervix. Failure of fusion may extend to the cervix, resulting in a complete bicornuate uterus, or may be partial, causing a milder abnormality (Fig. 18-13D). Several studies suggest that women with a bicornuate uterus can expect reasonable success in delivering a living child (about 60 percent). Rock (1977) reported that a bicornuate uterus was present in 55 percent of women with an anomalous uterus who had a satisfactory reproductive history. Only 14 percent of women with poor reproductive performance had a bicornuate uterus. As with many uterine anomalies, premature delivery is a substantial obstetric risk. Heinonen and colleagues (1982) reported a 28-percent abortion rate and a 20-percent incidence of premature labor in women with a partial bicornuate uterus. Women with a complete bicornuate uterus had a 66-percent incidence of preterm delivery and a lower fetal survival rate.

DIAGNOSIS AND TREATMENT

Hysterosalpingography is the initial diagnostic step in evaluating a possible bicornuate uterus. Classically, the uterine horns show a marked divergence, but various morphologic results are possible (see Fig. 19-7A). Because HSG may not accurately distinguish a bicornuate from a septate uterus, additional testing is necessary to make a definitive diagnosis. For example, sonography has been used successfully to differentiate the two. Malini (1984) reviewed 50 cases of uterine anomalies and compared sonographic findings with those obtained by HSG and laparoscopy. Sonography was confirmatory or diagnostic of the suspected anomaly in most cases (88 percent). Moreover, the diagnostic accuracy of sonography may be improved when coupled with HSG. Reuter and co-workers (1989) reported a diagnostic accuracy of 90 percent when the two techniques were used. A potentially more accurate method uses MR imaging (see Fig. 2-27). Pellerito (1992) evaluated uterine anomalies by MR imaging, and correctly identified all of 24 bicornuate uteri. Although fundal contour and septal conformation can be accurately visualized by MR imaging, its high cost precludes its use in all cases. Thus, sonography and HSG seem to be acceptable imaging techniques in the initial investigation. When the presumptive diagnosis is a septate uterus, laparoscopy is indicated for a definitive diagnosis and before hysteroscopic resection of the septum is initiated.

Surgical reconstruction of the bicornuate uterus has been advocated in women with multiple spontaneous abortions and in whom no other causative factors are identified. Strassman (1952) described the surgical technique that was designed to unify equal-sized endometrial cavities (Fig. 18-14B). Reproductive outcome after unification generally has been good. In 289 women, preoperative pregnancy loss was more than 70 percent. Following surgery, more than 85 percent of pregnancies ended in delivery of a viable infant. The actual benefit of metroplasty for a bicornuate uterus, however, has not been tested in a controlled clinical series. As in surgery for uterine didelphys, metroplasty should be reserved for women in whom recurrent pregnancy loss occurs with no other identifiable cause. Cesarean delivery is indicated following metroplasty to avert uterine rupture during labor.

FIGURE 18-14



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Methods of septate and bicornuate uterus repair. **A.** Wedge excision of a septate uterus. **B.** Strassman technique repair of a bicornuate uterus. **C.** Tompkin technique repair of a septate uterus. *(Modified from Rock, 1992, with permission.)*

Septate Uterus

PATHOPHYSIOLOGY AND REPRODUCTIVE OUTCOME

After lateral fusion of the mÃ¼llerian ducts, failure of their medial segments to regress can create a permanent septum within the uterine cavity. Its contours can vary widely and depends on the amount of persistent midline tissue. For example, the septum can project minimally from the uterine fundus or can extend completely to the cervical os (Fig. 18-13E). Moreover, septa can develop segmentally, resulting in partial communications of the partitioned uterus (Patton, 1994). The histologic structure of septa ranges from fibrous to fibromuscular.

The true incidence of these anomalies is not known because they are usually only detected in women with obstetric complications.

Although this defect does not predispose to increased rates of preterm labor or cesarean delivery, septate uterus is associated with a marked increase in spontaneous abortion (Heinonen, 2006). Woelfer and colleagues (2001) reported a first-trimester spontaneous abortion rate for septate uterus of 42 percent. Moreover, early pregnancy loss is significantly more common with a septate than with a bicornuate uterus (Proctor, 2003). For example, Buttram and Gibbons (1979) noted pregnancy loss rates in the first 20 weeks of 70 percent for bicornuate uterus compared with 88 percent for septate uteri.

This high pregnancy wastage likely results from partial or complete implantation on the largely avascular septum. This diminished blood supply, in combination with distortion of the uterine cavity and associated cervical or endometrial abnormalities, has been implicated. Based on operative experience for septal defects, the blood supply to the fibromuscular septum appears markedly reduced compared with that of normal myometrium. Altered patterns of vascularity in specimens of septal mucosa observed by Candiani and associates (1990) also reinforces the idea that pregnancy loss may be related to impaired embryo growth associated with septal implantation.

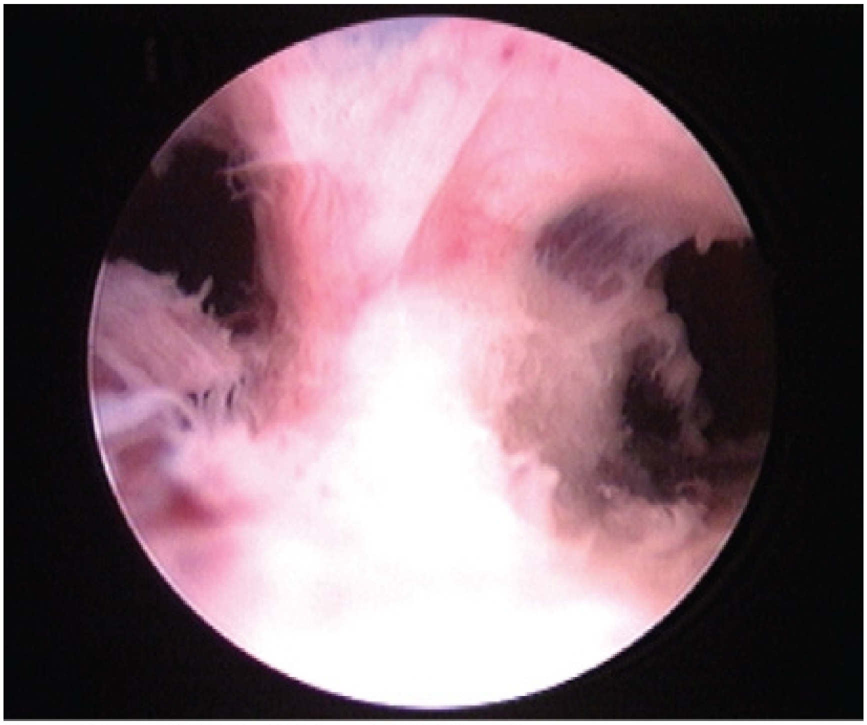
In addition to spontaneous abortion, septate uterus may infrequently cause fetal malformation. Heinonen (1999) described three newborns with a limb-reduction defect born to women with septate uterus.

DIAGNOSIS AND TREATMENT

Diagnosis of the septate uterus follows guidelines established for the bicornuate uterus and includes HSG and sonography (see Fig. 19-5B). Prior to widespread use of minimally invasive hysteroscopic procedures, abdominal metroplasty for septate uterus was shown to dramatically decrease fetal wastage and ultimately improve fetal survival (Figs. 18-14A and 18-14C) (Blum, 1977; Rock, 1977). Two main disadvantages to metroplasty include the recommendation for cesarean delivery to prevent uterine rupture, and the high rate of postoperative pelvic adhesion formation and subsequent infertility. A review by Bennet (1987) indicated a 30-percent incidence of infertility after abdominal metroplasty, but others have reported normal postoperative fecundity rates.

Currently, hysteroscopic septum resection is an effective and safe alternative to treat women with septate uterus (Fig. 18-15) (see Section 41-39, Septoplasty). Typically, operative hysteroscopy is combined with laparoscopic surveillance to reduce the risk of uterine perforation. After the initial case reports by Chervenak and Neuwirth (1981), many investigators have confirmed satisfactory live birth rates with the procedure (Daly, 1983; DeCherney, 1983; Israel, 1984). In a retrospective review, Fayez (1986) evaluated reproductive outcome in women who had either an abdominal metroplasty or hysteroscopic septoplasty. In this comparative analysis, an 87-percent live birth rate was reported in the hysteroscopic group, compared with a 70-percent rate in the abdominal group. Similarly, Daly and associates (1989) reported impressive results after hysteroscopic surgery. In 51 women, 47 had a total of 79 pregnancies. Only 6 percent gave birth prematurely, and 70 percent delivered at term. Moreover, proponents of the hysteroscopic procedure indicate that it reduces the risk of pelvic adhesions, shortens postoperative convalescence, lessens morbidity, and obviates the mandate for cesarean delivery (Patton, 1994).

FIGURE 18-15



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Hysteroscopic photograph of a uterine septum. The flesh-colored septum divides the endometrial cavity into halves. *(Courtesy of Dr. Kevin Doody.)*

Arcuate Uterus

An arcuate uterus is only a mild deviation from the normally developed uterus (Fig. 18-13F). Some clinicians report no impact on reproductive outcomes. Conversely, Woelfer and colleagues (2001) found excessive second-trimester losses and preterm labor. Surgical resection is indicated only if excessive loss is encountered and other etiologies for recurrent spontaneous abortion have been excluded.

ACQUIRED UTERINE DEFECTS

Defects in uterine structure and function may develop from exposure to diethylstilbestrol (DES); from intrauterine adhesion formation, termed *Asherman syndrome;* or from neoplastic growth, such as leiomyomas. These acquired uterine defects are recognized as contributors to pregnancy loss, and the spectrum of reproductive difficulties seen with these acquired defects mirrors that seen with congenital anomalies.

Diethylstilbestrol-Induced Reproductive Tract Abnormalities

REPRODUCTIVE TRACT FINDINGS

Diethylstilbestrol (DES), a synthetic nonsteroidal estrogen, was prescribed for an estimated 3 million pregnant women in the United States from the late 1940s through the early 1960s. Early reports claimed that the drug was useful in treating abortion, preeclampsia, diabetes, and preterm labor. It was unfortunately ineffective for these indications. Almost 20 years later, Herbst and co-workers (1971) found that DES exposure in utero was linked to the later development of vaginal clear cell adenocarcinoma in exposed female fetuses. The risk of this vaginal malignancy is about 1 per 1,000 exposed daughters. Subsequently, it was established that these daughters also had increased risks of developing cervical intraepithelial neoplasia as well as small cell cervical carcinoma (Herbst, 2000).

Additionally about one third have vaginal adenosis. During normal development, the vagina is originally lined by a glandular epithelium derived from the mÃ¼llerian ducts. By the end of the second trimester, this layer is replaced by squamous epithelium extending up from the urogenital sinus. Failure of the squamous epithelium to completely line the vagina is termed adenosis. Its clinical appearance is varied and may appear red, punctuate, and granular. Symptoms most often reported include vaginal irritation, discharge, and metrorrhagia, in particular, postcoital bleeding. Moreover, adenosis is noteworthy for its frequent association with vaginal clear cell adenocarcinoma.

In addition to carcinogenesis, several non-neoplastic abnormalities of the genitourinary tract following DES exposure in utero have become apparent. For example, as many as one fourth of women exposed to DES in utero have identifiable structural variations in the cervix and vagina. These include transverse septa, circumferential ridges involving the vagina and cervix, and cervical collars (see Fig. 32-7). Women with cervicovaginal abnormalities are more likely to have uterine anomalies, and half of all exposed women have uterine cavity anomalies evident on HSG. Significantly smaller uterine cavities, shortened upper uterine segments, and T-shaped and irregular cavities have been described (Fig. 18-13G) (Barranger, 2002). Additionally, abnormalities of the fallopian tubes have been noted, including shortened and narrowed dimensions and absence of fimbria. Hysterosalpingography remains the primary imaging procedure for the identification of these anomalies.

Males who were exposed to DES in utero also have structural abnormalities and cryptorchidism, testicular hypoplasia, microphallus, and hypospadias have been reported (Hernandez-Diaz, 2002). Moreover, Klip and colleagues (2002) provided evidence suggesting a transgeneration effect, in which male fetuses conceived by daughters of DES-exposed women have increased rates of hypospadias.

REPRODUCTIVE OUTCOME

In general, women exposed to DES have impaired conception rates (Goldberg, 1999; Palmer, 2001; Senekjian, 1988). Reduced fertility in these women is poorly understood but is associated with cervical hypoplasia and atresia. Of those who do conceive, the incidence of spontaneous pregnancy loss, ectopic pregnancy, and preterm delivery are increased, again particularly in those with associated structural abnormalities (Goldberg, 1999). For example, Herbst and colleagues (1989) reported the risk of ectopic pregnancy to be 7 percent in DES-exposed women, compared with none in a control group. Tubal anomalies resulting from DES exposure are the most likely cause, but associated decreased uterine size may also be a factor. In contrast, increases in preterm delivery rates probably result from uterine and cervical anomalies (deHaas, 1991; Herbst, 2000). Cervical incompetence is associated with mid-pregnancy losses and preterm delivery in these women (Ludmir, 1987). In 5 of 21 pregnancies, Michaels and co-workers (1989), using serial sonographic examinations, documented preterm cervical effacement and dilatation.

Asherman Syndrome

PATHOPHYSIOLOGY AND CLINICAL FINDINGS

Asherman syndrome is an infrequently found acquired uterine disorder characterized by intrauterine adhesions (see Figs. 16-2 and 41-41.1). Theories concerning the pathogenesis of this intrauterine scarring are based on several clinical observations. Specifically, in a series of 1856 women with Asherman syndrome, 88 percent were associated with postabortal or postpartum uterine curettage, indicating that direct endometrial trauma is a key factor (Schenker, 1982). In addition, occult infection and retained pregnancy tissue may be contributory (Rabau, 1963).

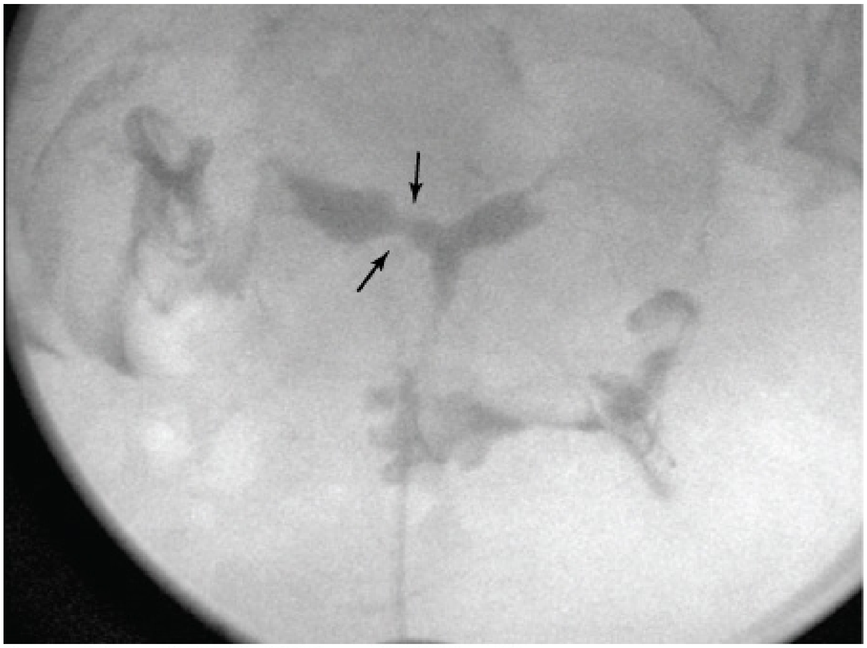
Classically, menstrual disorders and infertility are the presenting hallmarks of Asherman syndrome. Changes in menstrual patterns, such as amenorrhea or hypomenorrhea, are common and found in approximately 75 percent of women with this syndrome. Recent evidence, however, shows that women with Asherman syndrome may also present primarily with pregnancy loss. In their evaluation of 292 women with intrauterine adhesions, Schenker and Margalioth (1982) noted delivery of term pregnancies in only 30 percent of 165 pregnancies. The remainders either were spontaneously aborted (40 percent) or delivered prematurely. Pregnancy loss or prematurity may result from impaired implantation secondary to the intrauterine fibrosis and endometrial inflammation that is frequently observed with this syndrome.

DIAGNOSIS AND TREATMENT

When the syndrome is suspected, HSG is indicated. Of technical note during the procedure, rapid filling of the uterine cavity with

radiopaque contrast media may obscure adhesion detection. For this reason, Patton (1994) suggested using a water-soluble medium, slow incremental injections, image intensification, and multiple views to increase the procedure's sensitivity. Intrauterine adhesions characteristically appear as irregular, angulated filling defects within the uterine cavity (Fig. 18-16). The spectrum of scarring can range from isolated defects to complete obliteration of the uterine cavity. At times, uterine polyps, leiomyomas, air bubbles, and blood clots may masquerade as adhesions. Transvaginal sonography or saline-infusion sonography may help clarify these difficult cases, but a definitive diagnosis requires hysteroscopy (see Fig. 2-18).

FIGURE 18-16



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Hysterosalpingogram of a patient with Asherman syndrome. This image is digitally reversed, with the radiopaque contrast medium appearing black against a radiolucent background. Irregular filling defects (**arrows**) are seen within the endometrial cavity. *(Courtesy of Dr. Kevin Doody.)*

When the diagnosis of Asherman syndrome is confirmed, hysteroscopic lysis of adhesions is the preferred surgical treatment and is described in Section 41-41, Lysis of Intrauterine Adhesions. Prior to the introduction of operative hysteroscopy, dilatation and curettage was employed. Although effective in lysing intrauterine adhesions, this blind procedure unfortunately also injured normal endometrium. In contrast, the direct inspection afforded by hysteroscopy allows precise division of adhesion bands, clear documentation of the location and degree of adhesions, and the results of the operative repair. As with uterine septum resection, laparoscopy may be a necessary adjunct in moderate or severe cases to reduce the risk of perforation and intraperitoneal injury.

Direct comparisons between curettage and hysteroscopy have been difficult because they are based primarily on historic reviews of surgical series. Despite limitations to this type of data analysis, the collective results suggest that hysteroscopic methods are superior. For example, following the use of curettage, Schenker (1982) noted that 69 percent of women delivered at term, 8 percent delivered prematurely, and 10 percent suffered obstetric complications, including placenta accreta. In comparison, using hysteroscopy, Shaffer (1986) reported a similar term pregnancy rate (67 percent), but premature delivery rates of only 2 percent and obstetric complications in 3 percent. March and Israel (1981) reported impressive results after hysteroscopic surgery, with a postoperative term delivery rate of 87 percent. Moreover, reproductive outcome is excellent even when severe intrauterine adhesions are identified. Valle and Sciarra (1988) reported a term delivery rate of 79 percent in 14 women who conceived after surgery, despite severe adhesions. In addition, a 94-percent term delivery rate was observed in this series when mild adhesions

were present.

Uterine Leiomyomas

Uterine leiomyomas are the most common pelvic tumors in women, and accordingly, these acquired uterine defects pose a significant problem in both obstetrics and gynecology. A fuller discussion of the diagnosis and treatment of these growths is found in Chapter 9, Leiomyomas.

CERVICAL DEFECTS

Cervical Agenesis

Because of the common mÃ¼llerian source, women with congenital absence of the cervix typically also lack the upper vagina. The uterus, however, usually develops normally.

These patients initially present similarly to patients with other obstructive anomalies, that is, with primary amenorrhea and cyclic abdominal or pelvic pain. If a functional endometrium is present, a patient may have a distended uterus, and endometriosis may have developed secondary to retrograde menstrual flow. A single midline uterine fundus is the norm, although bilateral hemi-uteri have also been described (Dillon, 1979).

Radiographic studies, sonography, and MR imaging are helpful in evaluating the anatomy. If imaging demonstrates an obstructed uterus, hysterectomy has been recommended by Rock (1984). In contrast, Niver (1980) reported creation of an epithelialized endocervical tract and vagina in three patients. Significant morbidity, including infection, recurrent obstruction, and death due to sepsis, however, has been reported with establishment of such a vaginal-uterine connection by Casey (1997). Alternatively, conservative management with oral contraceptive pills may be used to suppress retrograde menses and possible endometriosis until a patient is ready to evaluate reproduction options. Thus, the uterus may be retained for possible reproductive potential. For example, Thijssen and associates (1990) reported a successful pregnancy using zygote intrafallopian tube transfer in a patient with cervical agenesis.

Cervical Stenosis

Cervical stenosis may result from congenital or acquired conditions and most commonly involves the internal os. Congenital cervical stenosis is likely due to segmental mÃ¼llerian hypoplasia. In contrast, postoperative scarring from cone biopsy, infection, neoplasia, and atrophic or radiation changes can lead to acquired cervical stenosis.

Symptoms of stenosis in menstruating women include dysmenorrhea, abnormal bleeding, amenorrhea, and infertility. Postmenopausal women are usually asymptomatic until there is an accumulation of fluid, exudates, or blood. The terms hydrometra (fluid), pyometra (exudate), or hematometra (blood) are used to describe these conditions and are discussed additionally in Chapter 9, Hematometra. The diagnosis is made on physical examination by an inability to introduce a dilator into the uterine cavity. If the obstruction is complete, a soft, enlarged uterus is palpable.

Management of cervical stenosis involves dilatation of the cervix with dilators of sequentially increasing diameter. Sonographic guidance may be useful to avoid uterine perforation, especially in postmenopausal women. Endometrial sampling is essential in these women to exclude endometrial hyperplasia or cancer.

OVARIAN ANOMALIES

A *supernumerary ovary* is an ectopic ovary that has no connection with the broad, utero-ovarian, or infundibulopelvic ligaments (Wharton, 1959). This rare gynecologic anomaly may be located in the pelvis, retroperitoneum, para-aortic area, colonic mesentery, or omentum. Aberrant migration of part of the gonadal ridge after the incorporation of germ cells describes one theorized schema. Arrest of these migrating germ cells in an ectopic site is followed by inductive formation of the surrounding tissue into ovarian stroma (Printz, 1973). Kuga (1999) described two cases of neonates found to have a supernumerary ovary resembling an omental cyst. Both supernumerary ovaries were detected by antenatal sonography, and the torsed cystic masses were removed by laparoscopy when the infants were 1 month. Mercer (1987) described two cases of supernumerary ovary presenting with adnexal masses that were separated from the ipsilateral ovary. Cystic teratoma and serous cystadenoma of the supernumerary ovary were found.

In contrast, the term *accessory ovary* is used when excess ovarian tissue is noted near a normally placed ovary and is connected to it. Wharton (1959) noted that both accessory ovary and supernumerary ovary were rare, finding approximately 1 case of accessory ovary in 93,000 patients and 1 case of supernumerary ovary in 29,000 autopsies. In Wharton's review, 3 of 4 patients with supernumerary ovary and 5 of 19 patients with accessory ovary had additional congenital defects, most frequently abnormalities of the genitourinary tract.

Unilateral ovarian absence is rare and describes the absence of one ovary, with or without the absence of the fallopian tube. It may result from a congenital malformation (agenesis or aplasia) or from ovarian torsion with necrosis and reabsorption, either antenatally or postnatally (Eustace, 1992; James, 1970). Mulayim (2003) reported a woman with a unicornuate uterus, unilateral ovary, and associated pelvic kidney. Mylonas (2003) reported 3 cases of ovarian agenesis and reviewed the literature, which contained descriptions of another 13 cases. The incidence has been suggested to be approximately 1 in 11,240 women (Sivanesaratnam, 1986).

FALLOPIAN TUBE ANOMALIES

The fallopian tubes develop from the unpaired distal ends of the mÃ¼llerian ducts and extend outward from the superolateral portion of the uterus. The fallopian tubes are between 10 and 14 cm long and normally end by curling around the ovary. A number of congenital and acquired defects of the fallopian tubes have been described by investigators and are discussed below. Disease may be asymptomatic or may be linked to infertility.

Congenital Tubal Disease

Congenital anomalies of the fallopian tube include accessory ostia, complete absence of the fallopian tube, and a number of embryonic cystic remnants (Woodruff, 1969). Remnants of the mesonephric duct in the female include a small structure called the *appendix vesiculosa;* and a few blind tubules in the broad ligaments, the *epoÃ¶phoron;* and a few blind tubules adjacent to the uterus collectively called the *paroÃ¶phoron* (see Fig. 18-2). The epoÃ¶phoron or paroÃ¶phoron may develop into cysts, and those of the epoÃ¶phoron are known as paraovarian cysts. Remnants of the mesonephric duct system are often present in the broad ligaments or are adjacent to the uterus or the vagina as Gartner duct cysts. Remnants of the paramesonephric (mÃ¼llerian) duct in the female may be seen as a small, blind paratubal cysts attached by a pedicle to the distal end of the fallopian tube, the hydatid of Morgagni.

Paratubal cysts are frequent incidental discoveries during gynecologic operations for other abnormalities or are found on sonographic examination (see Fig. 9-16). Most of these cysts are asymptomatic and slow growing and are discovered during the third and fourth decades of life.

In utero exposure to DES has been associated with various tubal abnormalities. Short, tortuous tubes or ones with shriveled fimbria and small ostia have been linked to infertility (DeCherney, 1981).

The congenital versus infectious etiology of salpingitis isthmica nodosa is unresolved. In this disorder, diverticula of the tubal mucosa in the isthmic region extend into the muscularis and to the serosa. It is commonly progressive and leads ultimately to tubal occlusion and infertility (Saracoglu, 1992). Salpingitis isthmica nodosa has also been associated with an increased risk of ectopic

pregnancy.

Acquired Tubal Disease

Acquired fallopian tube disease is due to inflammatory changes of infectious or noninfectious etiology. Infectious causes include pelvic inflammatory disease, tuberculosis or other granulomatous infiltration, ruptured appendix, postoperative infections, or sequela of septic abortion. Of these, pelvic inflammatory disease is the leading cause of tubal disease and is discussed in greater detail in Chapter 3, Pelvic Inflammatory Disease. Noninfectious causes include endometriosis, prior pelvic surgery, or salpingitis isthmica nodosa.

Regardless of the etiology, inflammatory response results in structural alteration and functional impairment of the fallopian tubes. Agglutination or obliteration of the fimbria leads to poor ova retrieval. More proximal obstructions may result from mucus plugs, scarring, and surgical interruption. Such obstructions can disrupt ova transport. In addition, denudation of the tubal epithelium and its cilia results in poor transit of gametes or embryos. Lastly, subfertility can be a consequence of the toxic environment created by intraluminal endometriosis or fluid from a hydrosalpinx.

Approximately one third to one fourth of all infertile women are diagnosed with tubal disease in developed countries (Serafini, 1989; World Health Organization, 2007). Individuals with tubal pathology usually present to the gynecologist or reproductive endocrinologist with complaints of infertility or symptoms of ectopic pregnancy. The HSG has been the traditional test for evaluating tubal status in infertile women, but the primary technique is laparoscopy with chromopertubation (see Figs. 19-5C and 19-8).

Involvement of the female reproductive tract with granulomatous disease is uncommon, but when found tends to involve the fallopian tube. The differential diagnosis of a histologic finding of epithelioid granulomas and giant cells includes tuberculosis (TB), sarcoidosis, brucellosis, leprosy, lymphogranuloma venereum, fungal infections, coccidioidomyocosis, and foreign body reactions (Boakye, 1997).

Tuberculosis continues to be a major cause of morbidity and mortality globally, and is found to be the second leading infectious cause of death among adults worldwide. The precise incidence of genital tuberculosis is difficult to ascertain, as a substantial proportion of cases are asymptomatic and inadvertently uncovered during investigation for infertility. In developing countries, genital TB may account for 3 percent or more of patients with infertility (Aliyu, 2004). In these cases, tubal damage and endometrial adhesions are the underlying cause. For example, the uterine cavity may be completely obliterated by adhesions, resulting in a condition that clinically mimics Asherman syndrome. A disorder in ovum transport further contributes to infertility. The likelihood of a return to fertility after anti-tubercular treatment is low, and in vitro fertilization with embryo transfer remains the most reliable approach to overcoming infertility associated with the disease (Aliyu, 2004).

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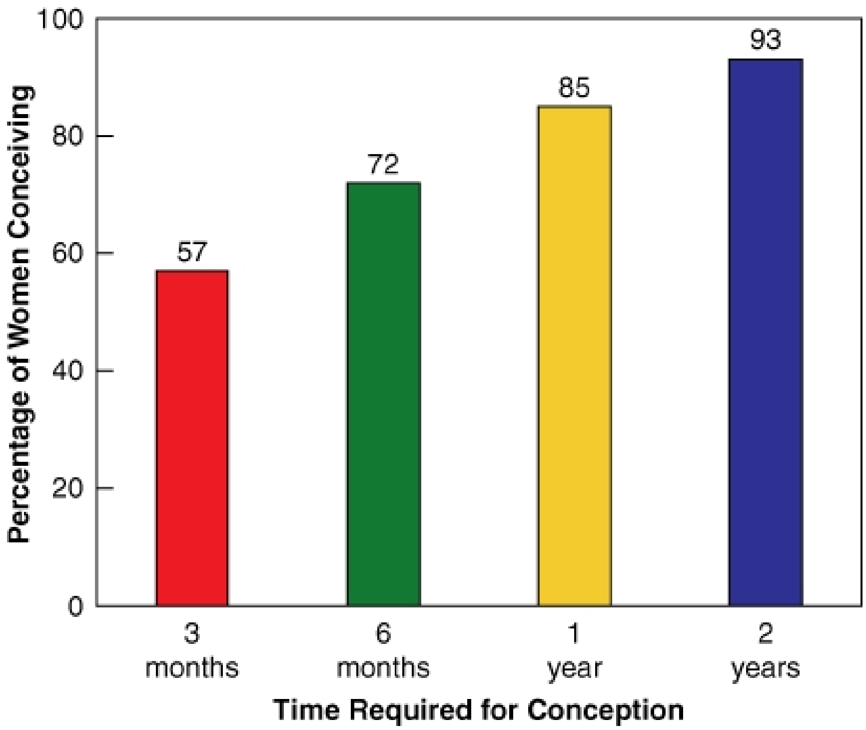
EVALUATION OF THE INFERTILE COUPLE: INTRODUCTION

The inability to conceive after 1 year of unprotected intercourse of reasonable frequency is termed infertility. It can be subdivided into *primary infertility* , that is, no prior pregnancies, and *secondary infertility* , referring to infertility following at least one prior conception. Conversely, *fecundability* is the ability to conceive, and data from large population studies have shown a monthly probability of conceiving of 20 to 25 percent. In those attempting conception, approximately 50 percent of women will be pregnant at 3 months, 75 percent will be pregnant at 6 months, and more than 85 percent will be pregnant by 1 year (Fig. 19-1) (Guttmacher, 1956; Mosher, 1991).

FIGURE 19-1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Time required for conception.

Thus, infertility is a common condition, affecting 10 to 15 percent of reproductive-aged couples. Of note, even without treatment, approximately half of women will conceive in the second year of attempting. This information can be reassuring to a couple. Although the prevalence of infertility is believed to have remained relatively stable during the past 40 years, there is no doubt that the demand for infertility evaluation and treatment has increased considerably (Abma, 1997; Hull, 1985; Stephen, 2000; Yao, 2002). The population boom following World War II produced a large group of women now entering the end of their reproductive

life span, many of whom have intentionally delayed pregnancy. Furthermore, with the well-publicized advances in infertility treatment, patients now have greater hope that medical intervention will help them achieve their goal.

Most couples are more correctly considered to be *subfertile,* rather than infertile, as they will ultimately conceive if given enough time. This concept of subfertility can be reassuring to couples. However, there are obvious exceptions, such as the woman with bilaterally obstructed fallopian tubes or the azoospermic male.

It is generally agreed that an infertility evaluation should be considered in any couple that has failed to conceive in 1 year. There are a number of clinical scenarios, however, in which evaluation should be considered sooner. For example, to delay evaluation in an anovulatory woman or a woman with a history of severe pelvic inflammatory disease (PID) may not be appropriate. Furthermore, it is clear that fecundability is highly age related, thus evaluation at 6 months should be performed in any woman older than 40 years, and according to some experts, in woman older than 35.

ETIOLOGY OF INFERTILITY

Successful pregnancy requires a complex sequence of events including ovulation, ovum pick-up by a fallopian tube, fertilization, transport of a fertilized ovum into the uterus, and implantation into a receptive uterine cavity. With male infertility, sperm of adequate number and quality must be deposited at the cervix near the time of ovulation. Remembering these critical events can help direct a clinician to develop an appropriate evaluation and treatment strategy.

In general, infertility can be attributed to the female partner one third of the time, the male partner one third of the time, and both partners in the remaining one third. This approximation emphasizes the importance of evaluating both members of the couple before instituting therapy. Estimates of the incidence of various causes of infertility are shown in Table 19-1 (Abma, 1997; Practice Committee of the American Society for Reproductive Medicine, 2006). Many of these diagnoses are discussed in greater detail in other chapters (Table 19-2).

Table 19-1 Etiology of Infertility	
Male	25%
Ovulatory	27%
Tubal/uterine	22%
Other	9%
Unexplained	17%

Table 19-2 Chapters with Relevant Information About Infertility			
Etiology	**Diagnosis**	**Chapter Title**	**Chapter Number**
Ovulatory dysfunction	PCOS	PCOS and hyperandrogenism	Chapter 17
	Hypothalamic-pituitary	Amenorrhea	Chapter 16
	Age-related	Menopausal Transition	Chapter 21
	POF	Amenorrhea	Chapter 16
Tubal disease	PID	Gynecologic Infection	Chapter 3
Uterine abnormalities	Congenital	Anatomic Disorders	Chapter 18
	Leiomyomas	Pelvic Mass	Chapter 9
	Asherman syndrome	Anatomic Disorders	Chapter 18
Other	Endometriosis	Endometriosis	Chapter 10

PCOS = polycystic ovarian disease; POF = premature ovarian failure; PID = pelvic inflammatory disease.

It should be strongly urged that both partners are present for the initial consultation. A visit to a health care provider for infertility evaluation provides an excellent opportunity for educating a couple regarding the normal process of conception. Many myths surround the ability to conceive, such as the importance of coital position and the need to remain horizontal following ejaculation. These myths can add undue stress to an already stressful situation and should be dispelled.

Couples should be educated regarding the concept of a *fertile window* for conception. The chance of conception is increased from the 5 days preceding ovulation through the day of ovulation (Wilcox, 1995). If the male partner has normal semen characteristics, a couple should have daily intercourse during this period to maximize the chance of conception. Although sperm concentrations will drop with increasing coital frequency, this decrease is not sufficient to negatively impact the chance of fertilization (Stanford, 2002). Couples should also be reminded to avoid oil-based lubricants, which are harmful to sperm.

MEDICAL HISTORY

The Female History

GYNECOLOGIC

As with any medical condition, a thorough history and physical examination is critical (American Society for Reproductive Medicine, 2000). For the female partner, questions should include a complete gynecologic history. Specifically, questions regarding menstruation (frequency, duration, recent change in interval or duration, hot flashes, and dysmenorrhea), prior contraceptive use, coital frequency, and duration of infertility should be asked. Also pertinent is a history of recurrent ovarian cysts, endometriosis, leiomyomas, sexually transmitted diseases, or pelvic inflammatory disease. Because prior conception indicates ovulation and a patent fallopian tube in the patient's past, this history should be sought. A prolonged time to conception may suggest borderline fertility and increase the chance of determining an etiology in a couple. Pregnancy complications such as miscarriage, preterm delivery, retained placenta, chorioamnionitis, or fetal anomalies should be noted. A history of abnormal Pap smears may be pertinent, particularly if a woman underwent cervical conization, which could impact cervical mucus quality and cervical competence (see Section 41-14, Cervical Conization).

When obtaining a medical history, it is critical to discuss coital history, including frequency and timing of intercourse. Symptoms such as dyspareunia may point to endometriosis and a need for earlier laparoscopic evaluation of the female partner.

MEDICAL

The medical history should be aimed at eliciting symptoms of hyperprolactinemia or thyroid disease. Symptoms of androgen excess such as acne or hirsutism may point to the presence of polycystic ovarian syndrome or much less commonly, congenital adrenal hyperplasia. Prior chemotherapy or pelvic irradiation may suggest the presence of ovarian failure.

SURGICAL

The surgical history should focus on pelvic and abdominal surgeries. Surgical treatment of ruptured appendicitis or diverticulitis should raise suspicion for the presence of pelvic adhesive disease or tubal obstruction or both.

MEDICATIONS

Medications should be noted including over-the-counter medications such as nonsteroidal anti-inflammatory drugs, that may adversely affect ovulation. In most instances, use of herbal remedies should be discouraged. Women should be encouraged to take a daily vitamin with at least 400 μg of folic acid to decrease the chance of neural-tube defects.

SOCIAL

A social history should focus on lifestyle and environmental factors such as eating habits and exposure to toxins. Abnormalities in gonadotropin-releasing hormone (GnRH) and gonadotropin secretion are clearly related to body mass indices greater than 25 or less than 17 (Table 1-7). (Grodstein, 1994a). Although difficult to achieve, even modest weight reductions in overweight women have been correlated with normalized menstrual cycles and subsequent pregnancies.

Accumulating data also suggest that cigarette smoking impacts fertility in both women and men (Hughes, 1996; Hull, 2000; Kunzle, 2003; Laurent, 1992; Stillman, 1986). The prevalence of infertility is higher, and the time to conception is longer in women who smoke, or even those exposed passively to cigarette smoke. Toxins in the smoke can accelerate follicular depletion and increase genetic mutations in gametes or early embryos (Sharara, 1994; Shideler, 1989). Admittedly, current data do not prove causation, but only correlation, between smoking and infertility or adverse pregnancy outcomes. Nevertheless, it is estimated that nearly 25 percent of women in the reproductive age group smoke, and the desire for pregnancy can be a powerful motivator toward cessation (Augood, 1998).

Alcohol consumption should also be limited. It is clear that heavy alcohol intake decreases fertility in women and has been associated with a decrease in sperm counts and increase in sexual dysfunction in men (Klonoff-Cohen, 2003; Nagy, 1986). A standardized alcoholic drink is typically defined as 12 ounces of beer, 5 ounces of wine, or 1.5 ounces of hard alcohol. Based on a number of studies, 5 to 8 drinks per week negatively impacts female fertility (Grodstein, 1994b; Tolstrup, 2003). As alcohol is also detrimental to early pregnancy, it is prudent to advise patients to avoid alcohol consumption while trying to conceive.

Caffeine consumption has also been linked to decreased fecundability. A cup of coffee contains approximately 115 mg of caffeine. Most studies suggest that consumption of more than 250 mg of caffeine daily by the female partner is associated with a modest, but statistically significant, decrease in fertility and increase in time to conception. Caffeine intake greater than 500 mg per day has also has been demonstrated to increase recurrent miscarriage rates (Bolumar, 1997; Caan, 1998; Cnattingius, 2000).

Illicit drugs may also impact fecundability. Marijuana suppresses the hypothalamic-pituitary-gonadal axis in both men and women, and cocaine can impair spermatogenesis (Bracken, 1990; Smith, 1987a). Although uncommon, fecundability is reduced with occupational exposure to the dry cleaning fluid perchloroethylene, and to toluene used in the printing business. Heavy metals and pesticides should also be avoided, as they may both decrease fertility rates as well as increase the risk of recurrent miscarriage (Orejuela, 1998).

ETHNICITY

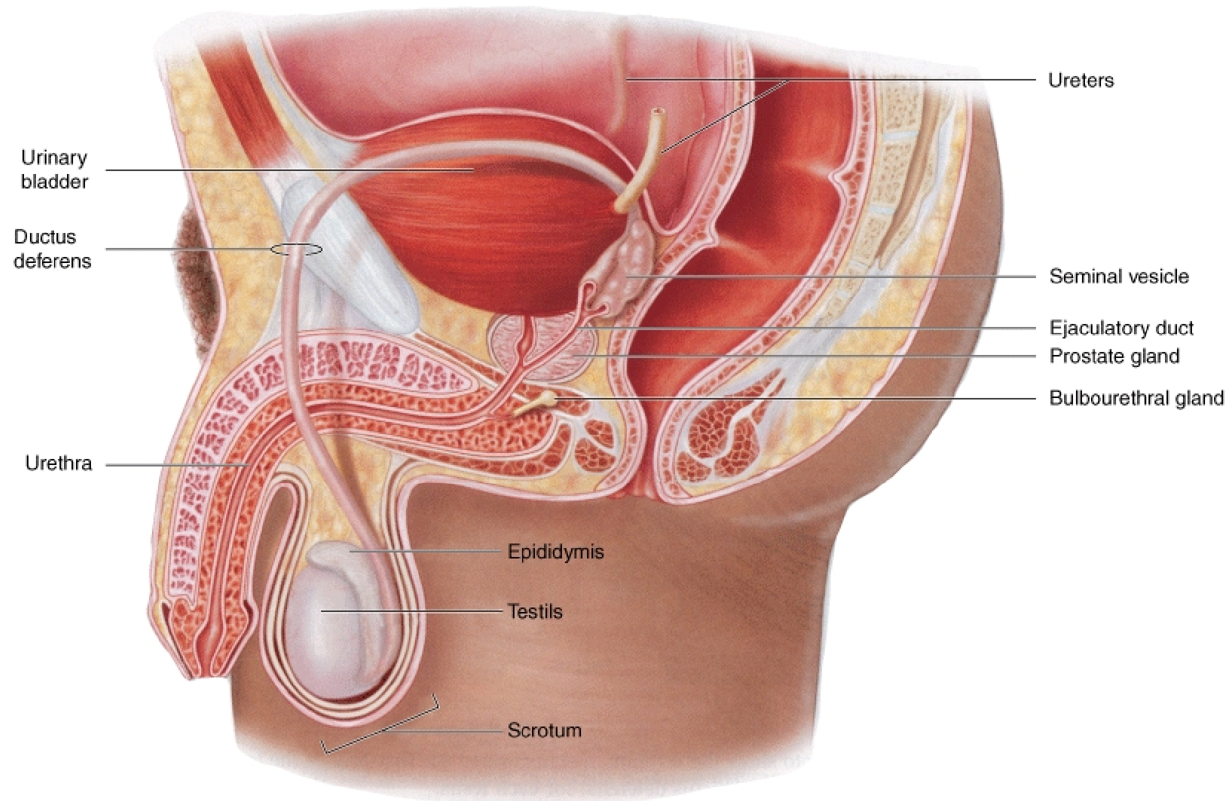
The ethnic background of both partners is important for determining the need for preconceptual testing, such as screening for sickle cell anemia in African-Americans, Tay-Sachs disease and other disorders in Ashkenazi Jews, and cystic fibrosis in patients of northern European descent (American College of Obstetricians and Gynecologists, 2004, 2005; Greenlee, 2003; Hruska, 2000). A family history of infertility, recurrent miscarriage, or fetal anomalies may also point to a genetic etiology. Although the inheritance pattern is complex, data suggest that both polycystic ovarian syndrome and endometriosis occur in familial clusters (see Chaps. 10,

Familial Clustering, and 17, Etiology). For example, it has been estimated that a woman carries a sevenfold increased risk of endometriosis over the general population if a single first-degree family member has the disease (Moen, 1993).

The Male History

The process of spermatogenesis, from stem cell to mature sperm, takes nearly 90 days, and therefore any detrimental event in the prior 3 months can adversely affect semen characteristics (Hinrichsen, 1980; Rowley, 1970). Spermatogenesis is optimal at temperatures slightly below body temperature, thus the location of the testes outside of the pelvis (Fig. 19-2). Illness with high fevers or chronic hot tub use can temporarily impair sperm quality. There is no definitive evidence that boxer underwear is advantageous (Tas, 1996).

FIGURE 19-2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Male genitalia. *(From McKinley, 2006, with permission.)*

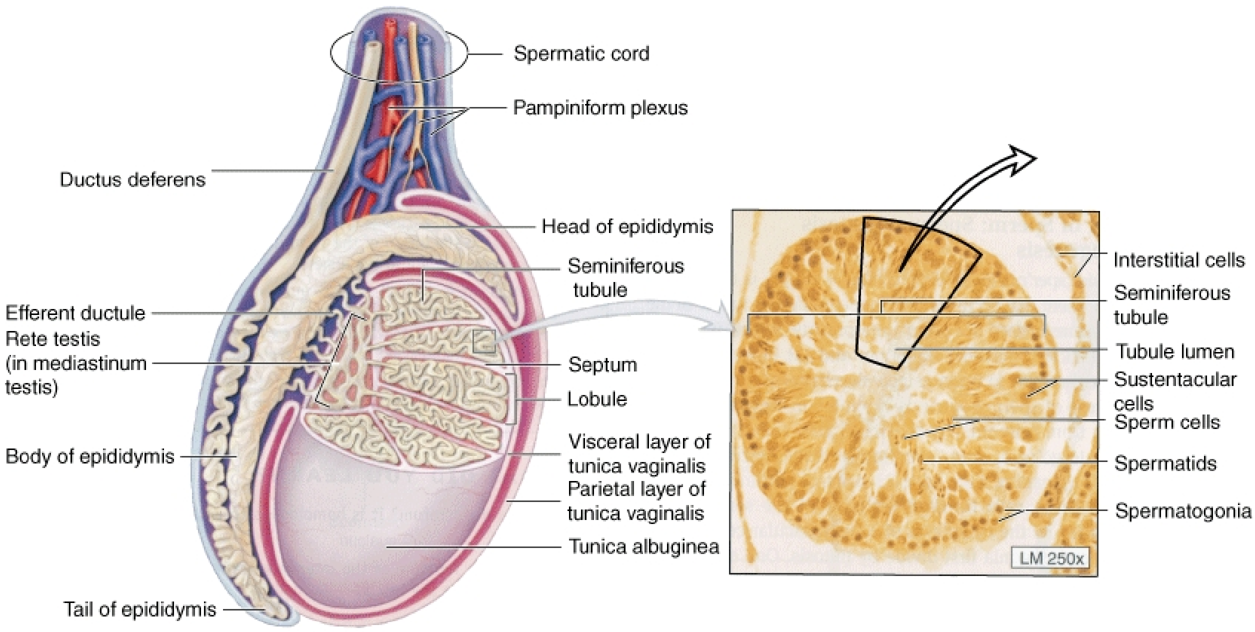
The male partner should be questioned regarding pubertal development and difficulties with sexual function. Erectile dysfunction, particularly in conjunction with decreased beard growth, may suggest decreased testosterone levels. Ejaculatory dysfunction should also be evaluated, including the presence of developmental anomalies such as hypospadias, which could result in suboptimal semen deposition (Benson, 1997).

Sexually transmitted diseases or frequent genitourinary infections, including epididymitis or prostatitis, may result in obstruction of the vas deferens. Mumps in an adult can result in testicular inflammation and damage to the spermatogenic stem cells (Beard, 1977). A history of cryptorchidism, testicular torsion, or testicular trauma may suggest the presence of abnormal spermatogenesis (Anderson, 1990; Bartsch, 1980; Sigman, 1997; Tas, 1996). Compared with fertile males, males with a history of unilateral or bilateral cryptorchidism have fertility rates of 80 percent and 50 percent, respectively (Lee, 1993). The reason for poor semen

characteristics in these patients is unclear. The relatively warm intra-abdominal temperature may cause permanent damage to the stem cells. Alternatively, genetic abnormalities that led to the abnormal location of the testes may also affect sperm production.

A history of varicocele should also be obtained. A varicocele consists of dilated veins of the pampiniform plexus of the spermatic cords that drain the testes (Figs. 19-3A). Varicoceles are believed to raise scrotal temperature, however, controversy exists regarding the impact of varicoceles on fertility (Chehval, 1992; Jarow, 2001; World Health Organization, 1992). Although 30 to 40 percent of men seen in infertility clinics are diagnosed with a varicocele, nearly 20 percent of men in the general population are similarly affected. There is also substantial disagreement on the benefits gained from varicocele repair, particularly for subclinical varicoceles, which are only detectable by sonography (Kim, 1999; Schlesinger, 1994; Steckel, 1993). Nevertheless, if a varicocele is suspected, it should be evaluated by a urologist, preferably one with a specific interest in infertility.

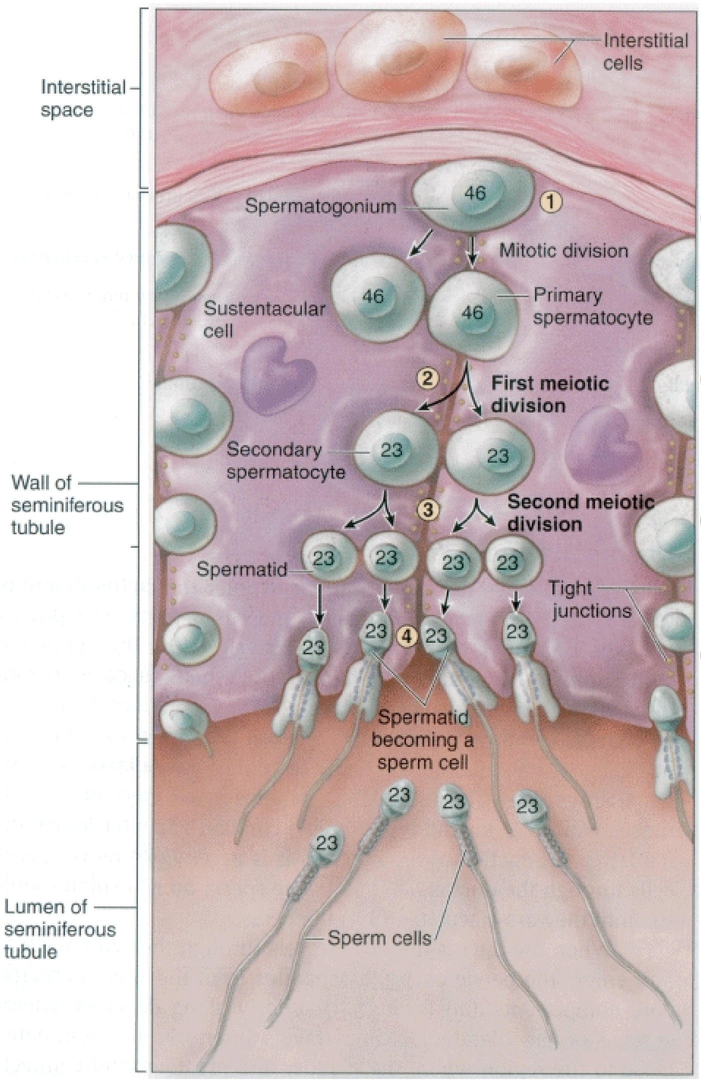
FIGURE 19-3



A Testis

B Seminiferous tubule

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



(1) Germ cells that are the origin of sperm cells are *diploid* (2n=46) cells called spermatogonia. Mitotic divisions of these cells produce a new germ cell and a committed cell. The committed cell is a primary spermatocyte.

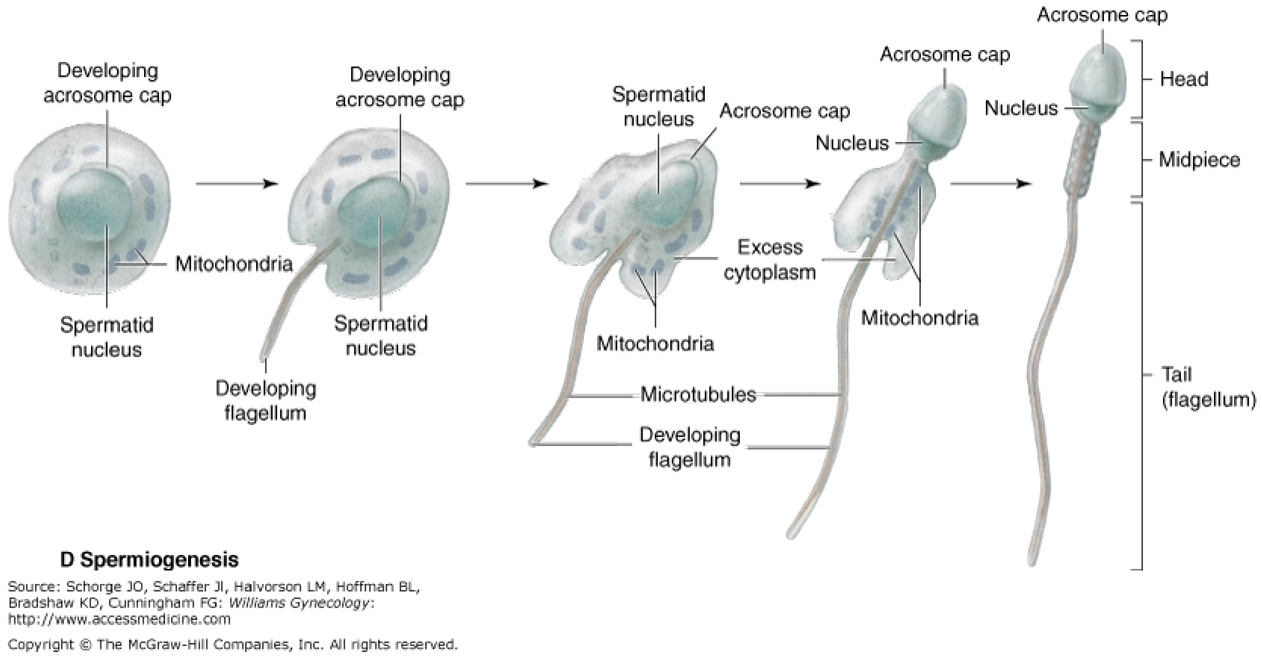
(2) The first meiotic division begins in the *diploid* primary spermatocytes. The *haploid* (n=23) cells produced by the first division are called secondary spermatocytes.

(3) The second meiotic division originates with the secondary spermatocytes and produces spermatids.

(4) The process of spermiogenesis results in morphological changes needed to form sperm cells that will be motile.

C Spermatogenesis

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



A. Gross anatomy of a testis. **B.** Cutaway of the testis reveals the microscopic structure of a seminiferous tubule. **C.** Cutaway of the seminiferous tubule shows the mitotic and meiotic divisions involved with spermatogenesis. **D.** Structural changes required during spermiogenesis, as sperm cells become spermatids. *(From McKinley, 2006, with permission.)*

The medical history should focus on prior treatment with chemotherapy or local radiation therapy that may damage the spermatogonial stem cells. Hypertension, diabetes mellitus, and neurologic disorders may be associated with erectile dysfunction or retrograde ejaculation. A number of medications are known to adversely impact semen parameters including cimetidine, erythromycin, gentamicin, tetracycline, and spironolactone (Sigman, 1997). As described above, cigarettes, alcohol, illicit drugs, and environmental toxins all adversely affect semen parameters (Muthusami, 2005; Ramlau-Hansen, 2007). The increasing use of anabolic steroids also decreases sperm production by suppressing the production of intra-testicular testosterone (Gazvani, 1997). Although the effects of many medications are reversible, anabolic steroid abuse may lead to lasting or even permanent damage to testicular function.

PHYSICAL EXAMINATION

Examination of the Female Patient

A physical examination may provide many clues to the cause of infertility. Vital signs, height, and weight should be recorded. Hirsutism, alopecia, or acne indicates the need to measure androgen levels. The presence of acanthosis nigricans is consistent with insulin resistance associated with polycystic ovarian syndrome or much less commonly, Cushing syndrome. Additionally, thyroid abnormalities should be noted. The evaluation and treatment of endocrine abnormalities that impact reproductive function are described in greater detail in Chapters 16, Evaluation and 17, Metabolic Syndrome and Cardiovascular Disease.

A pelvic exam may be particularly informative. Inability to place a speculum through the introitus may raise doubts about coital frequency. The vagina should be moist and rugated, and the cervix should have a reasonable amount of mucus, both indicating adequate estrogen production. An enlarged or irregularly shaped uterus may reflect leiomyomas, whereas a fixed uterus suggests the presence of pelvic scarring due to endometriosis or prior pelvic infection. Uterosacral nodularity or ovarian masses may additionally implicate endometriosis.

All women should have a normal Pap smear result within the year preceding treatment. Negative cultures for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* should be obtained to ensure that cervical manipulation during evaluation and treatment does not cause an ascending infection. The breast examination must be normal, and when indicated by age or family history, a mammogram should be obtained prior to initiating hormonal treatment.

Examination of the Male Patient

Most gynecologists will not feel comfortable performing a complete physical examination of the male. Nevertheless, parts of this evaluation are relatively easy to perform, and a gynecologist at minimum should understand the primary focus of the examination. As signs of testosterone production, normal secondary sexual characteristics such as beard growth, axillary and pubic hair, and perhaps male pattern balding should be present. Gynecomastia or eunuchoid habitus may suggest Klinefelter syndrome (47,XXY karyotype) (De Braekeleer, 1991).

The penile urethra should be at the tip of the glans for proper semen deposition in the vagina. Testicular length should be at least 4 cm with a minimal testicular volume of 20 mL (Charny, 1960; Hadziselimovic, 2006). Small testes are unlikely to be producing normal sperm numbers. The presence of a testicular mass may indicate the presence of testicular cancer, which can present as infertility. The epididymis should be soft and nontender to exclude chronic infection (see Fig. 19-2). Epididymal fullness can suggest obstruction of the vas deferens. The prostate should be smooth, nontender, and normal size. Additionally, the pampiniform plexus of veins should be palpated for varicocele (Jarow, 2001). Importantly, both vas deferens should be palpable. Congenital bilateral absence of the vas deferens is associated with mutation in the gene responsible for cystic fibrosis (Anguiano, 1992).

EVALUATION FOR SPECIFIC CAUSES OF INFERTILITY

The infertility evaluation can be conceptually simplified into confirmation of: (1) ovulation, (2) normal female reproductive tract anatomy, and (3) normal semen characteristics. The specifics regarding evaluation of each of these categories will be detailed in the following sections and is shown in Table 19-3.

Table 19-3 Infertility Testing

Etiology	Evaluation
Ovulatory dysfunction	Serum midluteal progesterone Ovulation predictor kit Early follicular FSH Â± estradiol level (ovarian reserve) Â± Serum measurements (TSH, prolactin, androgens) Â± Ovarian sonography (antral follicle count) Â± Basal body temperature chart Â± Endometrial biopsy (luteal phase defect)
Tubal/pelvic disease	Hysterosalpingography Laparoscopy with chromotubation
Uterine factors	Hysterosalpingography Transvaginal sonography Saline-infusion sonography Magnetic resonance imaging Hysteroscopy Laparoscopy
Cervical factor	Â± Postcoital test
Male factor	Semen analysis

FSH = follicle-stimulating hormone; TSH = thyroid-stimulating hormone.

Etiology of Infertility in the Female

OVULATORY DYSFUNCTION

Ovulation may be perturbed by abnormalities within the hypothalamus, anterior pituitary, or ovaries. Hypothalamic disorders may be due to lifestyle, for example, excessive exercise, eating disorders, or stress. Alternatively, dysfunction or improper migration of the hypothalamic gonadotropin-releasing hormone neurons may be inherited, such as that which occurs in idiopathic hypothalamic hypogonadism (IHH) or Kallman syndrome (see Chap. 16, Hypogonadotropic Hypogonadism). Thyroid disease and hyperprolactinemia may also contribute to menstrual disturbances. A full discussion of disorders that result in menstrual disturbances are discussed in Chapter 16.

Menstrual Pattern

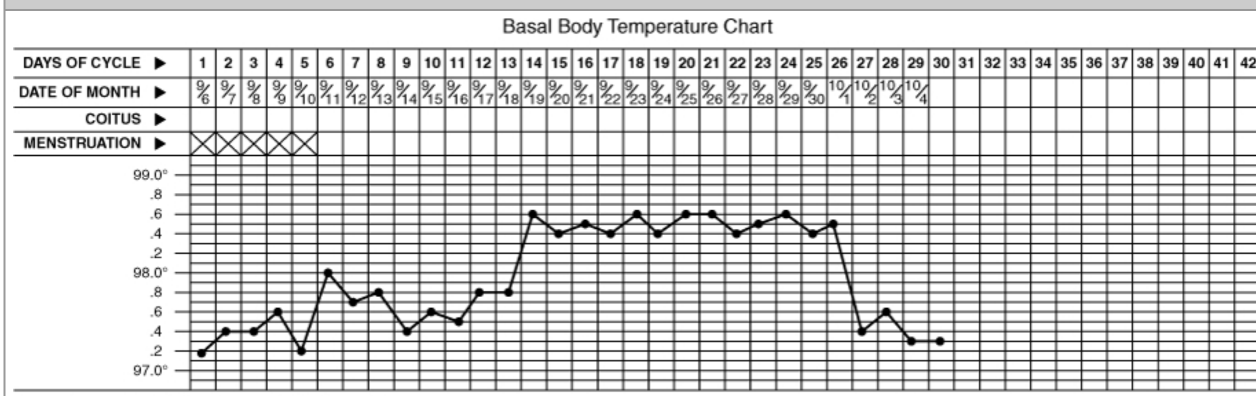
A patient's menstrual history is an excellent predictor of regular ovulation. A woman with cyclic menses at an interval of 25 to 35 days and duration of bleeding of 3 to 7 days is most likely ovulating. Although there is a wide variation in these numbers, each woman will have her own normal pattern. Therefore, these figures should not significantly vary across cycles for an individual woman.

Probable ovulation is also suggested by the presence of *mittelschmerz,* which is midcycle pelvic pain associated with ovulation, or moliminal symptoms such as breast tenderness, acne, food cravings, and mood changes. Ovulatory cycles are more likely to be associated with dysmenorrhea, although severe dysmenorrhea may suggest the presence of endometriosis.

Basal Body Temperature

Basal body temperature (BBT) charting has long been used to identify ovulation. This test requires that a woman's morning oral temperature be graphically charted. Oral temperatures are usually 97.0Â° to 98.0Â°F during the follicular phase. A postovulatory rise in progesterone levels increases basal temperature by approximately 0.4Â° to 0.8Â°F. This *biphasic* temperature pattern is strongly predictive of ovulation (Bates, 1990). Nevertheless, although this test has the advantage of being inexpensive, it is insensitive in many women. Furthermore, for a couple wishing to conceive, the temperature increase follows ovulation, and therefore the window of maximal fertility has been missed (Grinsted, 1989; Luciano, 1990; Moghissi, 1992). Although this test may be useful for a couple first attempting to conceive, it has generally fallen out of favor as an infertility diagnostic tool (Fig. 19-4).

FIGURE 19-4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Biphasic pattern seen on this basal body temperature chart suggests ovulation. *(From Chang, 2005, with permission).*

Ovulation Predictor Kits

A number of additional tests for ovulation have been developed. Urinary ovulation predictor kits are widely available in pharmacies.

These kits, which measure the concentration of urinary luteinizing hormone (LH) by colorimetric assay, have become relatively easy to use and provide clear instructions regarding interpretation.

In general, a woman should begin testing 2 to 3 days prior to the predicted LH surge, and testing should be continued daily. There is no clear consensus regarding the optimal time of day to test. Some infertility specialists suggest that the concentrated first morning void is a logical testing time, whereas others are concerned that this sample may demonstrate a false-positive or equivocal result. Other clinicians reason that the serum LH peak occurs in the morning and that the greatest likelihood of detecting a urinary peak would be in the late afternoon or evening. Timing is probably not critical as long as the test is performed daily, as the LH surge spans only 48 to 50 hours. In most instances, ovulation will occur the day following the urinary LH peak (Luciano, 1990; Miller, 1996).

If equivocal results are obtained, the test can be repeated in 12 hours. In one study, urine LH surge assays were estimated to have 100-percent sensitivity and 96-percent accuracy, although this is undoubtedly an overestimate of typical-use results (Grinsted, 1989; Guermandi, 2001).

Serum Progesterone

Ovulation can also be tested by measuring midluteal phase serum progesterone levels. In a classic 28-day cycle, serum is obtained on cycle day number 21 following the first day of menstrual bleeding, or 7 days following ovulation. Levels during the follicular phase are generally <2 ng/mL. Values above 4 to 6 ng/mL are highly correlated with ovulation and subsequent progesterone production by the corpus luteum (Guermandi, 2001). Progesterone is secreted as pulses, and therefore a single measurement is not indicative of overall production during the luteal phase. As a result, an absolute threshold for acceptable progesterone levels has not been clearly established. Nevertheless, Hull and colleagues (1982) have reported that a midluteal progesterone concentration of greater than 9.4 ng/mL is predictive of higher pregnancy rates than those observed in patients with progesterone levels less than 10 ng/mL.

Many clinicians choose to empirically treat any patient with a progesterone level below this value with natural progesterone. Although this approach is unlikely to be harmful, the utility of this management is unproven. Accordingly, the midluteal progesterone level is best regarded as an excellent measure for the occurrence of ovulation, but not an absolute indicator of adequate luteal function.

Endometrial Biopsy

Adequate progesterone levels are required for endometrial preparation prior to implantation. Inadequate progesterone levels are believed to result in luteal phase defect (LPD). Thus, it was proposed that an endometrial biopsy would represent both the function of a corpus luteum as well as the endometrial response, thereby providing more clinically relevant information than a serum progesterone level alone. Noyes and associates (1975) described a sequence of histologic events in the endometrium in the periovulatory, luteal, and early menstrual stages. These investigators defined LPD as a lag in the histologic appearance of the endometrium of greater than 2 days relative to the actual day of the cycle. This discrepancy in dating is termed an *out-of-phase biopsy* . Classically, an endometrial biopsy is obtained as close to the impending menstrual cycle as possible based on previous cycle length, and more recently, on the timing of the LH surge.

Unfortunately, the utility of this test is severely hampered by high intra-observer and inter-observer variability (Balasch, 1992; Scott, 1993). The estimated frequency of LPD in the infertile population has ranged widely, but is generally agreed to be between 5 and 10 percent. Nevertheless, it appears that a finding of an out-of-phase biopsy occurs nearly as frequently in fertile as in infertile women, with a large overlap in incidence between the two groups (Aksel, 1980; Balasch, 1992; Davis, 1989; Scott, 1993). This observation has led many experts to conclude that LPD may not exist as a clinical entity. Certainly in its current form, the endometrial biopsy has little predictive value. For all of these reasons, this test is no longer considered a routine part of the infertility evaluation.

It is interesting to note that impressive advances are being made in our understanding of the timing of protein expression in the endometrial glands and stroma. Potential markers for uterine receptivity include osteopontin, cytokines (leukemia inhibitory factor, colony-stimulating factor-1, and interleukin-1), cell adhesion molecules (the integrins), and the L-selectin ligand, which has been

proposed to mediate embryo attachment (Carson, 2002; Kao, 2003; Lessey, 1998). In the future, endometrial biopsies may again become part of the diagnostic evaluation if expression patterns of these proteins prove to be predictive of endometrial receptivity.

Sonography

Serial ovarian sonography can demonstrate the development of a mature antral follicle and its subsequent collapse during ovulation. This approach is rather time consuming and ovulation can be missed. However, sonography is an excellent approach for supporting the diagnosis of polycystic ovarian syndrome with its associated oligo-anovulation Fig. 17-11).

FEMALE AGING AND OVULATORY DYSFUNCTION

Epidemiology

There is a clear inverse relationship between female age and fertility (Table 19-4). A classic study was performed in the Hutterites, a community that eschews contraception. After ages 34, 40, and 45, the incidence of infertility was 11 percent, 33 percent, and 87 percent, respectively. The average age at last pregnancy was 40.9 years (Tietze, 1957). Another interesting study evaluated cumulative pregnancy rates in women using donor insemination. In women less than 31 years old, 74 percent achieved pregnancy within 1 year. These rates fell to 62 percent for women between 31 and 35 years, and further declined to 54 percent in women older than 35 (Treloar, 1998).

Table 19-4 Female Aging and Infertility

Female Age (years)	Infertility
20â€"29	8.0%
30â€"34	14.6%
35â€"39	21.9%
40â€"44	28.7%

Physiology

Age-related infertility is most closely linked to the loss of viable oocytes. At midgestation, a normal human female fetus has approximately seven million oocytes, which will decrease to between two and three million by birth (see Fig. 14-1). Ongoing atresia of nondominant follicles proceeds throughout a woman's reproductive life span, with approximately 300,000 follicles at puberty and <1,000 follicles at the onset of menopause. Thus, even before a female reaches menarche, she has lost most of her eggs. A fuller discussion of pubertal and menopausal physiology can be found in Chapters 14 and 21.

As a woman ages, there is a substantially increased risk of genetic abnormalities as well as mitochondrial deletions in the remaining oocytes (Keefe, 1995; Pellestor, 2003). These factors result in decreased pregnancy rates and increased miscarriage rates in both spontaneous and treatment cycles. The overall miscarriage risk in women older than 40 years has been estimated to be 50 to 75 percent (Maroulis, 1991).

The rate of follicular loss and age at menopause varies between women and is likely genetically determined. For example, a family history of early menopause is correlated with an increased risk of early menopause in an individual woman. In general, the age at last birth in naturally fertile populations averages 10 years prior to the menopause (Nikolaou, 2003; te Velde, 2002). However, in most cases, it is impossible to predict the onset of menopause, and therefore testing is indicated to determine current fertility potential in older women.

Follicle-Stimulating Hormone Levels

Measurement of serum follicle-stimulating hormone (FSH) levels in the early follicular phase is a simple and sensitive predictor of ovarian reserve (Toner, 1991). With declining ovarian function, the support cells (granulosa cells and luteal cells) secrete less inhibin, a peptide hormone which is responsible for inhibiting FSH secretion by the anterior pituitary gonadotropes (see Chap. 15,

Gonadotropins and Follicular Development). With loss of luteal inhibin, FSH levels rise in the early follicular phase. Measurement of serum FSH levels is classically completed on cycle day number 3 following the onset of menses. A value greater than 10 mIU/mL indicates significant loss of ovarian reserve and should prompt a more rapid evaluation and more intensive treatment. In a large study evaluating in vitro fertilization cycles, a day-3 FSH level exceeding 15 mIU/mL was predictive of significantly lower pregnancy rates (Muasher, 1988; Scott, 1995; Toner, 1991).

Estradiol Levels

Many clinicians also measure serum estradiol levels simultaneously (Buyalos, 1997; Licciardi, 1995). Addition of an estradiol measurement may decrease the incidence of false-negative results of FSH values alone. Somewhat paradoxically, despite the overall depletion of ovarian follicles, estrogen levels in older women will be elevated early in the cycle due to increased stimulation of ovarian steroidogenesis by elevated FSH levels. A cycle-day-3 estradiol level of >80 pg/mL is considered abnormal. It should be noted that reference levels for estradiol and FSH can vary between laboratories. Therefore, every clinician should become familiar with their own laboratory's normal values.

Clomiphene Citrate Challenge Test

The clomiphene citrate challenge test (CCCT) is believed to be a more sensitive indicator of diminished ovarian reserve than measurement of "unstimulated" hormone levels (Navot, 1987). Clomiphene citrate is a nonsteroidal estrogen receptor modulator. Although the exact mechanism is not fully understood, clomiphene is believed to block the negative feedback inhibition of endogenous estrogens on FSH secretion. (see Fig. 20-1). With the test, a woman takes 100 mg of clomiphene citrate orally on cycle day numbers 5 through 9. Estradiol and FSH levels are measured on day 3, and an FSH level is measured on day 10. Follicle-stimulating hormone elevations at either time point are indicative of diminished ovarian reserve.

In general, a simple day-3 FSH level measurement is probably adequate as an initial screen. However, consideration should be given to performing a CCCT in any woman with a borderline FSH level or who is older than 40 years. Moreover, an FSH or CCCT should be strongly considered in any woman with a history of ovarian surgery, chemotherapy, or irradiation. Testing may also be done in those with a smoking history, poor response to gonadotropins, age greater than 35 years, or a family history of early menopause.

Sonography

Additional methods of evaluating ovarian reserve are under study. One of the best validated is the use of transvaginal sonography to measure ovarian volume and obtain an early follicular phase antral follicle count (Frattarelli, 2000). The number of small antral follicles reflects the size of the resting follicular pool. Less than 10 antral follicles predicts poor response to gonadotropin stimulation.

Testing Interpretation

Abnormal testing through any of the above methods correlates consistently with a poor prognosis for achieving pregnancy whatever the woman's age. Conversely, a normal test does not negate the impact of a woman's age on her fertility status. This information may be useful in counseling a couple about prognosis. Poor results in an older woman can supply an impetus to either attempt donor oocyte in vitro fertilization (IVF), or pursue alternatives such as adoption. Borderline results in a younger woman may suggest a need for a more intensive approach.

TUBAL AND PELVIC FACTORS

Symptoms such as chronic pelvic pain or dysmenorrhea may suggest the presence of tubal obstruction or pelvic adhesions or both. Adhesions can prevent normal tubal movement, ovum pick-up, and transport of the fertilized egg into the uterus. A wide variety of etiologies may contribute to tubal disease, including pelvic infection, endometriosis, and prior pelvic surgery.

A history of pelvic inflammatory disease (PID) is highly suspicious for damage to the fallopian tubes or the presence of pelvic adhesions. In the United States, the most common causes of tubal disease are infection with *Chlamydia trachomatis* or *Neisseria gonorrhoeae,* whereas tuberculosis is a common cause of both tubal and intrauterine disease in countries with endemic infection and should be considered in immigrant populations. Tubal infertility has been estimated to follow in 12 percent, 23 percent, and 54

percent of women following one, two, or three cases of PID, respectively (Lalos, 1988). Nevertheless, a lack of PID history is not overly reassuring, as nearly one half of patients who are found to have tubal damage have no history of antecedent disease (Rosenfel, 1983).

Inflammation and chronic bleeding within implants of endometriosis can also lead to obstruction of fallopian tubes or development of severe pelvic adhesions. In addition, a history of ectopic pregnancy, even if treated medically with methotrexate, implies the likelihood of significant tubal damage. Residual adhesions are common after even the most meticulous pelvic surgery, particularly in cases of pelvic inflammation, due to the presence of blood, infection, or the irritation caused by the contents of mature cystic teratomas (dermoids).

Testing for tubal patency can be performed by hysterosalpingography (HSG) or by chromotubation during laparoscopy. Chapter 2, Hysterosalpingography contain additional discussion of HSG performance. Fimbrioplasty may be considered in cases of distal tubal obstruction without significant hydrosalpinx. Attempts may also be made to correct proximal obstruction with balloon tuboplasty via hysteroscopy. However, with the advent of successful pregnancy rates using IVF, tubal surgery rates are decreasing.

UTERINE ABNORMALITIES

Congenital Anomalies

Uterine anomalies can be either inherited or acquired. As described in Chapter 18, Incidence and Classification, inherited anomalies include uterine septum, bicornuate uterus, unicornuate uterus, and uterine didelphys. With the possible exception of a large uterine septum, the impact of these anomalies on conception has been difficult to verify, although a subset are clearly associated with pregnancy complications. As a uterine septum can now be removed relatively simply and safely with hysteroscopy, most infertility specialists will proceed with surgery if this anomaly is identified.

Diethylstibesterol

In utero exposure to this synthetic estrogen has been linked to malformations of uterine development in addition to an increased risk for vaginal adenosis. More information on this topic can be found in Chapter 18, Acquired Uterine Defects. The classic uterine appearance is a small, T-shaped uterus. This cohort of women is seen progressively less frequently in infertility clinics as they pass reproductive age (Goldberg, 1999).

Acquired Abnormalities

Acquired anomalies include intrauterine polyps, leiomyomas, and Asherman syndrome.

Endometrial Polyps

These soft fleshy growths are estimated to be present in 3 to 5 percent of infertile women (Farhi, 1995; Soares, 2000). The prevalence is higher in women with symptoms, such as intermenstrual or postcoital bleeding. Although these complaints typically prompt hysteroscopic removal, most data have not clearly demonstrated an indication for removing polyps in otherwise asymptomatic women (Ben-Arie, 2004; DeWaay, 2002). Of note, however, a recent study has suggested that removal of even small polyps (under 1 cm) may improve pregnancy rates following intrauterine insemination (Perez-Medina, 2005).

Leiomyomas

These benign smooth muscle tumors may also prevent normal implantation, depending on their size and location (Pritts, 2001). Certainly, it seems reasonable to assume that leiomyomas that obstruct a fallopian tube, distort the uterine cavity (submucosal leiomyomas), or fill the uterine cavity (intracavitary leiomyomas) would be detrimental to implantation. The endometrium overlying these tumors is less vascular and the surrounding myometrium exhibits dysfunctional contractility, both of which may contribute to decreased rates of successful pregnancy. It seems equally reasonable to postulate that a subserosal leiomyoma would not impact pregnancy. Additional discussion on this topic can be found in Chapter 9, Infertility and Pregnancy Wastage.

Farhi and colleagues (1995) studied the effects of uterine leiomyomas on IVF success rates. In 28 women with a normal uterine cavity, the pregnancy rate was 30 percent per embryo transfer. In 18 women with an abnormal cavity, the pregnancy rate was only 9 percent per transfer. Although this suggests that removal of submucous leiomyomas should improve fecundability, there are no randomized, prospective trials to confirm this conclusion.

Appropriate intervention is even more ambiguous in the patient with intramural leiomyomas that do not abut the endometrium (Stovall, 1998). Thus far, it has not been possible to develop an algorithm based on number, volume, or location of these tumors that accurately predicts the need to remove them, either to improve implantation rates or decrease pregnancy complications such as miscarriage, placental abruption, or preterm labor. Nevertheless, most experts will consider surgical removal of a leiomyoma greater than 5 cm or multiple smaller tumors in this size range. Surgical complications are discussed in atlas Section 41-18, Myomectomy. These include creation of Asherman syndrome following the removal of large submucosal leiomyomas or the need for cesarean delivery if the full myometrial thickness is transected.

Asherman Syndrome

The presence of intrauterine adhesions, also called *synechiae* , is termed *Asherman syndrome* . This diagnosis is discussed in detail in Chapter 18, Asherman Syndrome. Asherman syndrome occurs most frequently in women with a history of uterine dilation and curettage, particularly in the context of infection and pregnancy (Schenker, 1996). A woman with an intrauterine device (IUD) complicated by infection is also at high risk for the development of intrauterine adhesions. The clinical history will often include an acute postsurgical decrease in menstrual bleeding or even amenorrhea. Treatment of Asherman syndrome involves hysteroscopic lysis of the adhesions as described in atlas Section 41-41, Lysis of Intrauterine Adhesions. Although dilation and curettage has been used, hysteroscopy provides more precise control with less secondary scarring. Electrosurgical coagulation is rarely required, as the bands are in most cases composed of dense connective tissue with poor blood supply.

RADIOLOGIC AND SURGICAL APPROACHES FOR EVALUATION OF PELVIC STRUCTURES

There are five major approaches for evaluating pelvic anatomy: (1) hysterosalpingography, (2) transvaginal sonography with or without saline instillation, (3) hysteroscopy, (4) laparoscopy, and (5) pelvic imaging by magnetic resonance (MR) imaging. As shown in Table 19-5, each has its own advantages and disadvantages.

Table 19-5 Advantages and Disadvantages of Various Methods for Evaluating Pelvic Anatomy

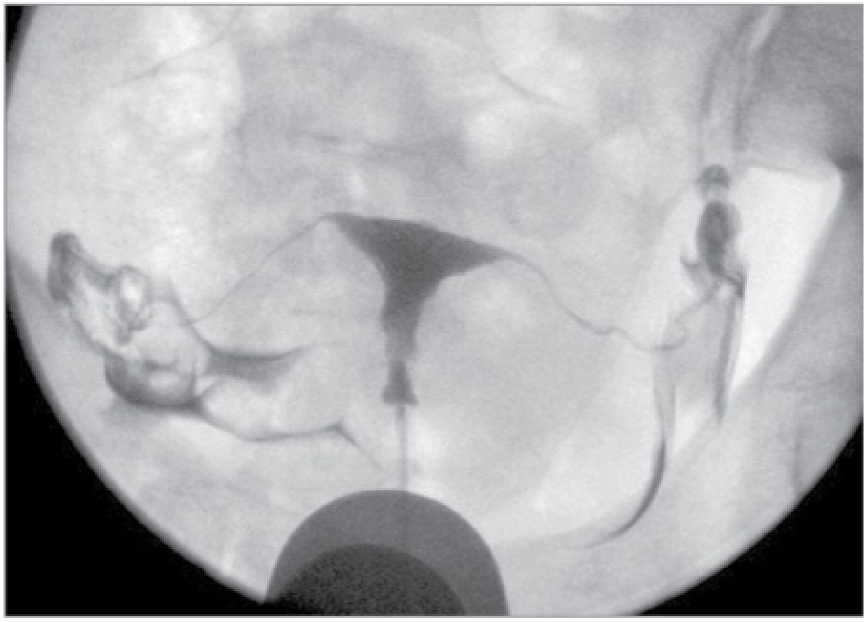
	Tubal Patency	Uterine Cavity	Developmental Defects	Endometriosis or PAD	Ovaries
HSG	+	+	â€“	+/â€“	â€“
SIS	â€“	+	+/â€“	â€“	+
MR imaging	â€“	+	+	â€“	+
Hysteroscopy	â€“	+	+ (with laparoscopy)	â€“	â€“
Laparoscopy	+	â€“	+ (with hysteroscopy)	+	+

HSG = hysterosalpingography; MR = magnetic resonance; PAD = pelvic adhesive disease; SIS = saline-infusion sonography.

Hysterosalpingography

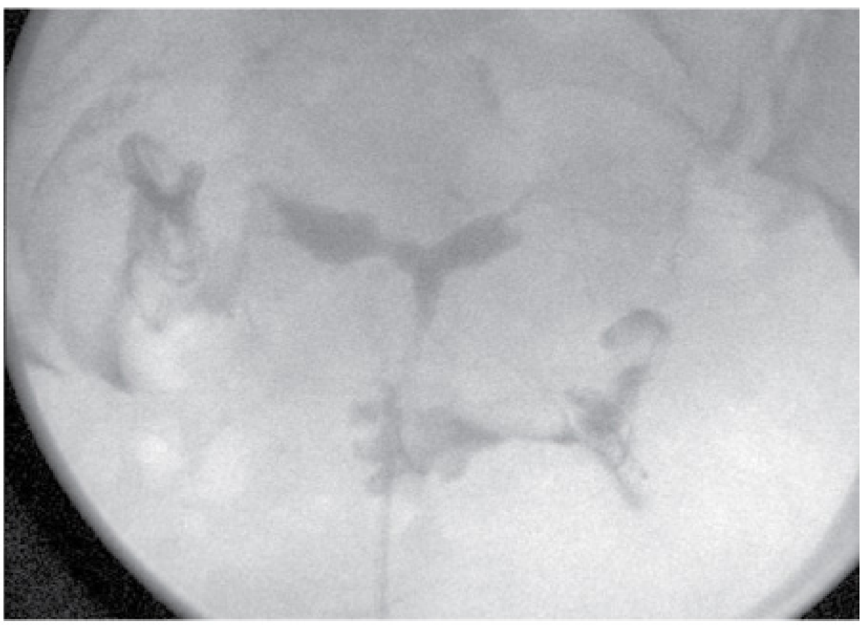
This radiographic tool can be useful for evaluating the shape and size of the uterine cavity, in addition to defining tubal status (see Chap. 2, Hysterosalpingography). Hysterosalpingography is generally performed on cycle day numbers 5 through 10. At this time, there should be minimal intrauterine clotting that could block tubal outflow or give the false impression of an intrauterine abnormality. Furthermore, a woman should not have ovulated and possibly conceived. For this test, iodinated contrast medium is infused through a catheter placed into the uterus. Under fluoroscopy, dye is followed as it fills the uterine cavity, then the tubal lumen, and finally spills out of the tubal fimbriae into the pelvic cavity (Fig. 19-5).

FIGURE 19-5



A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

C

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Hysterosalpingogram findings. These images are digitally reversed, causing the radiopaque contrast to appear black against a radiolucent background. **A.** Normal hysterosalpingogram. Radiopaque dye fills the uterine cavity and spills from both fallopian tubes into the peritoneal cavity. The dye catheter is seen beneath the endometrial contour. **B.** Asherman syndrome. Contrast dye fills a small and irregularly shaped endometrial cavity, often described as having a "moth-eaten" appearance. **C.** Bilateral hydrosalpinges. Note the marked tubal dilation and lack of spill of contrast medium at the fimbrial ends. *(Courtesy of Drs. Kevin Doody and Bala Bhagavath.)*

Tubal Disease

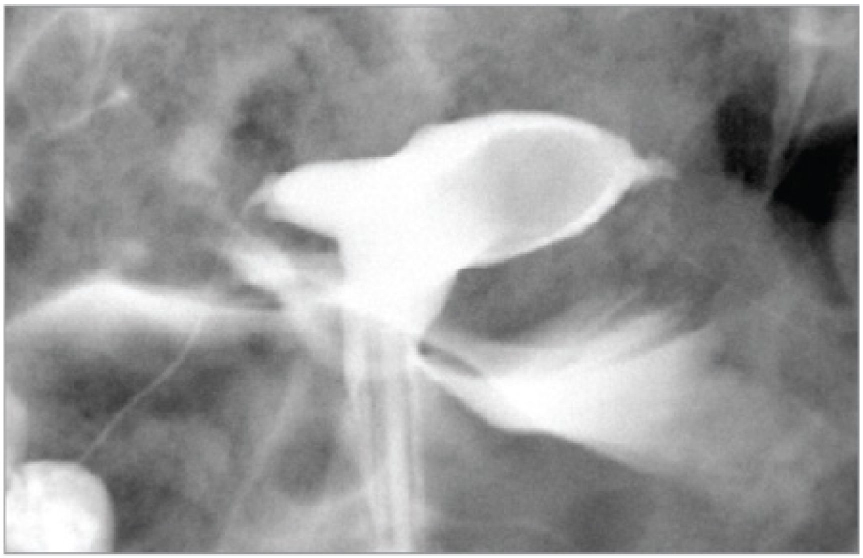
In a large meta-analysis, HSG was demonstrated to have 65-percent sensitivity and 83-percent specificity for tubal obstruction (Swart, 1995). Tubal contractions, particularly cornual spasm, can give the incorrect impression of proximal fallopian tube obstruction (a false-positive result). Much less commonly reported is a scenario in which a false-negative result is obtained when the fallopian tube is seen as patent by HSG, although subsequently it is determined to be blocked. Many causes of tubal disease affect both tubes, and therefore it is clinically unusual to have unilateral disease. Unilateral obstruction with a normal contralateral tube is most likely due to the dye following the path of least resistance during the HSG procedure, however, laparoscopy with chromotubation should be considered prior to treatment to confirm a final diagnosis.

Hysterosalpingography is not reliable in detecting peritubal or pelvic adhesions, although loculation of dye around the tubes may be suggestive (see Fig. 19-5). Thus, HSG is an excellent predictor of tubal patency, but is less effective at predicting normal tubal function or the presence of pelvic adhesions. Pregnancy rates have been reported to be increased following HSG, and have been suggested to result from flushing of intratubal debris. However, these reports followed evaluation with oil-based dyes rather than water-based dyes, which are currently preferred.

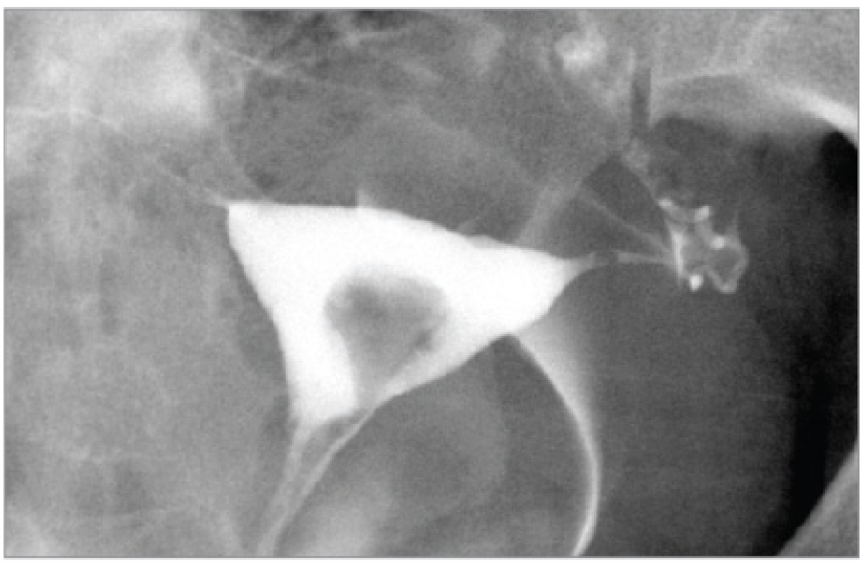
Uterine Pathology

Hysterosalpingography also provides analysis of the contour of the intrauterine cavity. A polyp, leiomyoma, or adhesion within the cavity will block dye diffusion, resulting in an intrauterine "defect" in dye opacity on radiograph (Fig. 19-6). False-positives may be obtained due to the presence of blood clots, mucus plugs, or shearing of the endometrium during placement of the intrauterine catheter.

FIGURE 19-6



A



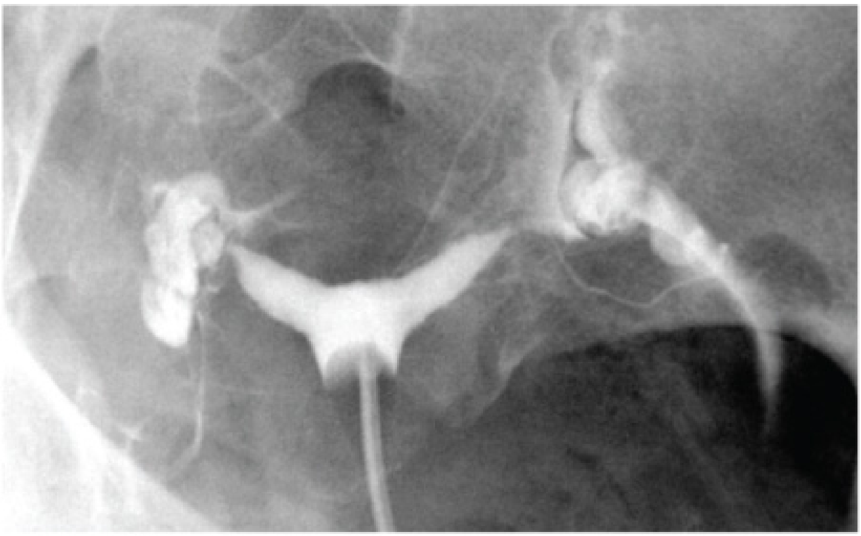
B

Appearance of leiomyoma and endometrial polyps on hysterosalpingogram (HSG). **A.** A broad-based filling defect is formed during HSG by a submucous leiomyoma. Note distortion of the left cornu by this mass. **B.** A more irregular filling defect is created by an endometrial polyp. Note that polyps generally have a less substantial attachment to the myometrium. *(Courtesy of Dr. Diane Twickler.)*

Hysterosalpingography can also define developmental uterine anomalies (Fig. 19-7). In general, developmental uterine anomalies are not causative for infertility, but may be associated with miscarriage or later fetal loss, creating a management dilemma. It may

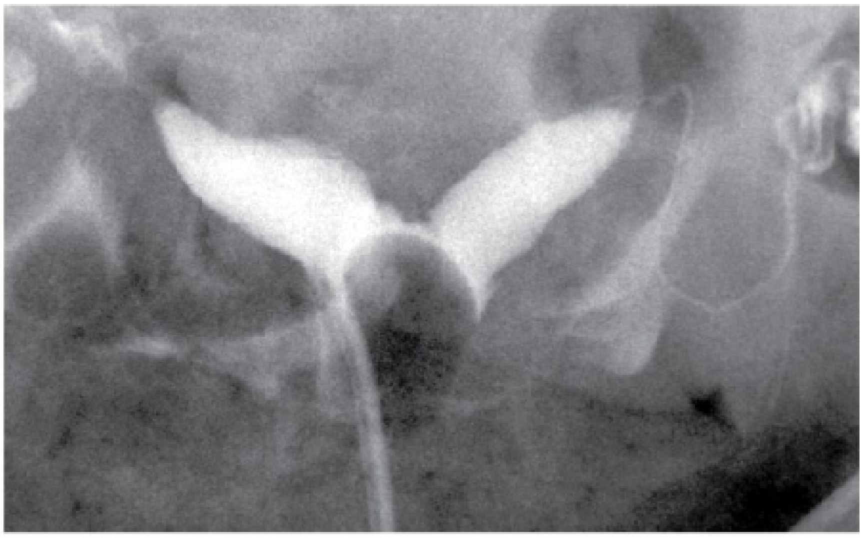
be reasonable to surgically treat a uterine anomaly in an effort to improve pregnancy outcome. However, a couple must be carefully counseled that fertility itself is unlikely to be affected. A further discussion of the fertility effects of congenital anomalies is found in Chapter 18, Incidence and Classification.

FIGURE 19-7



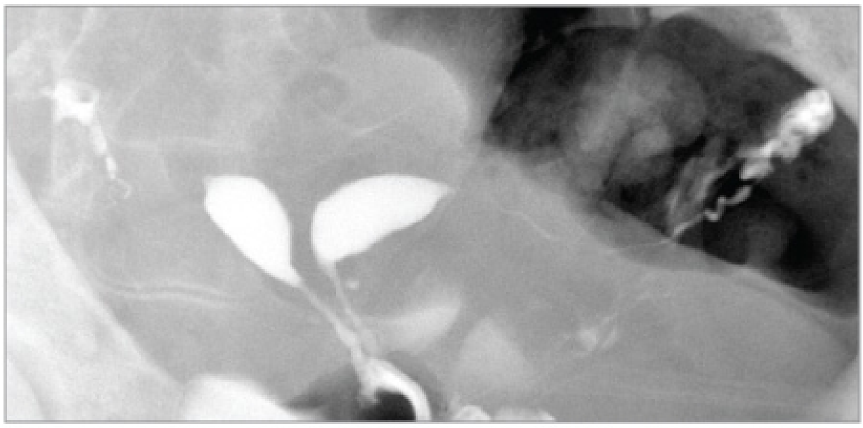
A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



C

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Hysterosalpingogram appearance of mÃ¼llerian developmental anomalies. **A.** Bicornuate uterus, due to a failure of fusion of the mÃ¼llerian ducts, produces a fundal defect with wide-spaced uterine horns. **B.** Septate uterus due to a failure of resorption. This moderate septum displaces the radiopaque dye to the level of the radiolucent injector balloon. C. Uterine didelphys consisting of two completely separate mÃ¼llerian systems including duplication of the cervix. *(Courtesy of Dr. Diane Twickler.)*

A Y-shaped uterus on hysterosalpingography may represent either a uterine septum or bicornuate uterus. In these cases, the external contour of the uterine fundus must be evaluated using MR imaging, high resolution sonography, or laparoscopy (see Fig. 2-27). A smooth fundal contour is consistent with a diagnosis of uterine septum. This is an important distinction, as a septum is often resected, but a bicornuate uterus is generally not treated.

Hysterosalpingography has been shown to accurately identify intrauterine pathology. In one study of over 300 women in which hysteroscopy was used as the gold standard, HSG was determined to be 98-percent sensitive and 35-percent specific, with a positive predictive value of 70 percent and a negative predictive value of 8 percent. Most misdiagnoses were due to an inability to distinguish polyps from submucous leiomyomas, a minimal problem, as these patients will undergo further evaluation and treatment in either case (Preutthipan, 2003; Randolph, 1986). Although other studies have not provided such impressive results, it is clear that HSG is a powerful tool for evaluation of the uterine cavity.

Sonography

Transvaginal pelvic sonography may also be helpful in determining uterine anatomy, particularly during the luteal phase, when the thickened endometrium acts as contrast to the myometrium. Although not yet widely available, the development of three-dimensional ultrasound machines is advancing the discriminatory abilities of sonography.

The infusion of saline into the endometrial cavity during follicular phase sonography provides another approach for achieving contrast between the cavity and uterine walls. This procedure has many names including saline ultrasound, hysterosonography, sonohysterography, or saline-infusion sonography (SIS). Details of this procedure are described in Chapter 2, Saline-Infusion Sonography. Saline-infusion sonography has been reported to have a sensitivity of 75 percent and specificity of over 90 percent. It has an acceptable positive predictive value of 50 percent and an excellent negative predictive value of 95 percent, which greatly exceeds the negative predictive value of HSG (Soares, 2000). Moreover, SIS may be more sensitive than HSG in determining whether a cavitary defect is a pedunculated leiomyoma or a polyp (Figs. 8-7 and 8-8). Perhaps more importantly, SIS can help determine what portion of a submucous leiomyoma is within the cavity, as only those with less than a 50-percent intramural component should be approached by hysteroscopy.

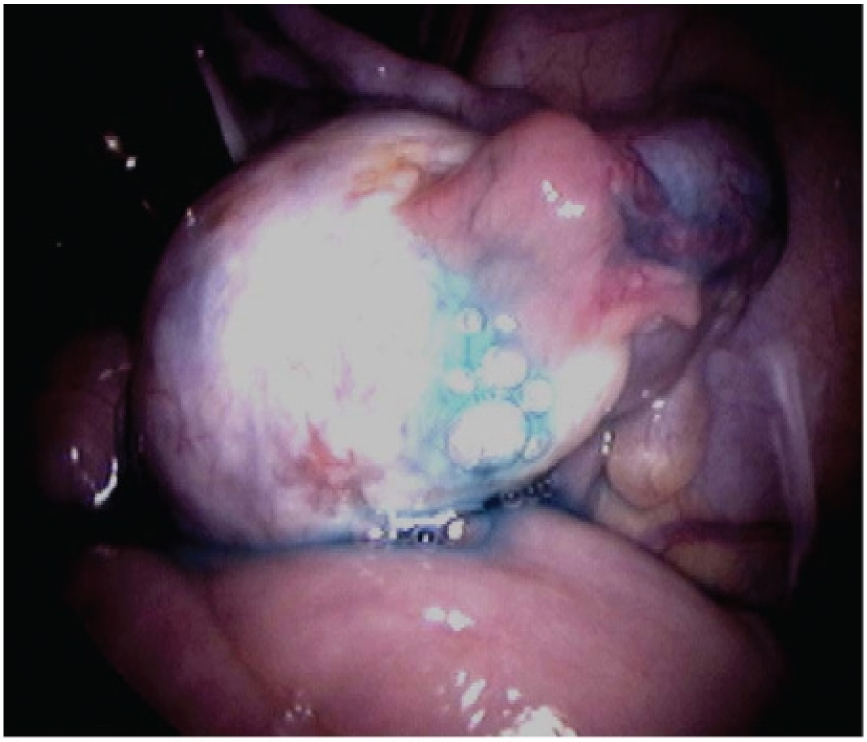
The primary limitation of SIS is that it does not provide information about the fallopian tubes, although rapid loss of saline into the pelvis is certainly consistent with at least unilateral patency. Saline-infusion sonography is generally less painful than HSG and

does not require radiation exposure. Therefore, it is the preferred method if information about tubal patency is not required, such as in patients who are known to require in vitro fertilization.

Laparoscopy

Direct inspection provides the most accurate assessment of pelvic pathology and laparoscopy is the gold standard approach. Chromotubation may be performed, and a dilute dye is injected through an acorn cannula placed against the cervix or a balloon catheter positioned within the uterus (see Figs. 41-28.4 and 41-28.5). Tubal spill is evaluated through the laparoscope (Fig. 19-8). Indigo carmine dye is preferable to methylene blue, as the latter rarely may induce acute methemoglobinemia, particularly in patients with glucose-6-phosphate dehydrogenase deficiency. Laparoscopy allows both diagnosis and immediate surgical treatment of abnormalities such as endometriosis or pelvic adhesions. Laparoscopic ablation of endometriotic lesions or adhesions may increase subsequent pregnancy rates.

FIGURE 19-8



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Chromotubation seen at laparoscopy. Note the spill of blue dye from the fimbriated end of the fallopian tube onto the ovarian surface. *(Courtesy of Dr. Kevin Doody.)*

As laparoscopy is an invasive procedure, it is not advocated in place of HSG as part of the initial infertility evaluation. Exceptions include women with a history or symptoms suggestive of endometriosis or pelvic inflammation. However, even in these women a preliminary HSG may be informative (De Hondt, 2005).

If laparoscopy is clearly indicated, then hysteroscopy can also be performed while the patient is under anesthesia to evaluate the uterine cavity. Moreover, in operative hysteroscopic cases, laparoscopy can help direct surgery and avoid perforation, for example, during septal incision.

Laparoscopy also may be considered in patients who fail to conceive with clomiphene or gonadotropin ovulation induction. If pelvic disease is found and treated, progression to IVF may be avoided. With improvements in IVF success rates, this latter argument is

becoming less justifiable, as the cost of surgery well exceeds the cost of an IVF cycle.

Hysteroscopy

Endoscopic evaluation of the intrauterine cavity is the primary method for defining intrauterine abnormalities. Hysteroscopy can be performed in an office or operating room. With improved instrumentation, the ability to concurrently treat abnormalities in the office is increasing, however, substantially more extensive hysteroscopic surgery is possible in an operating room setting. A fuller discussion of hysteroscopy and its indications is found in atlas Section 41-35, Hysteroscopy.

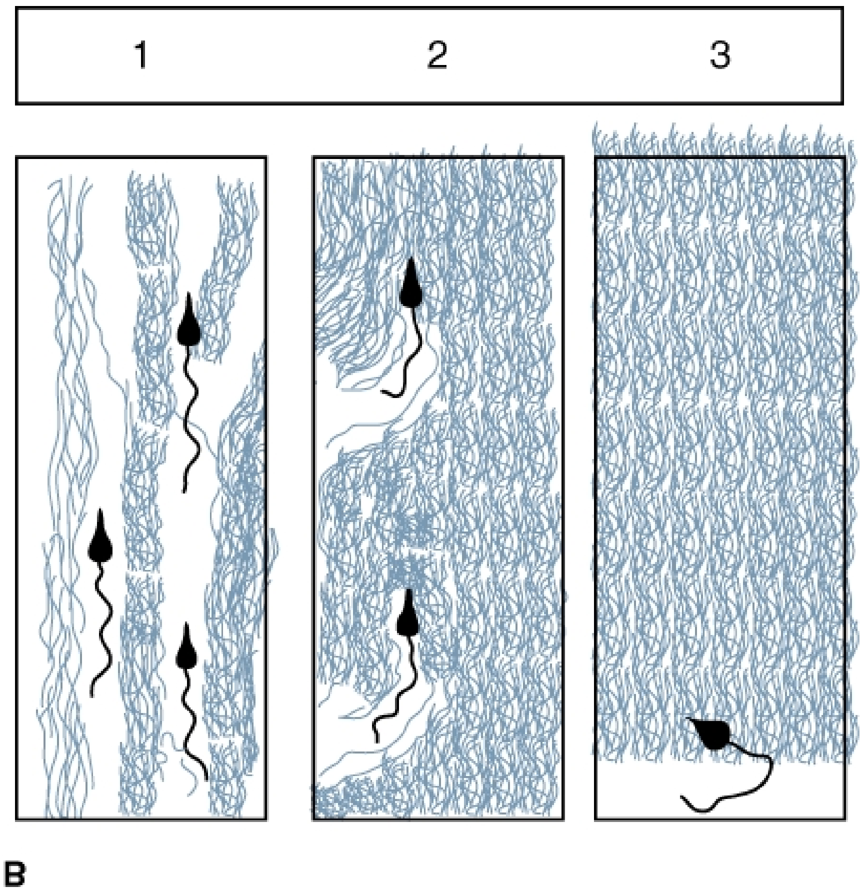
CERVICAL FACTORS

The cervical glands secrete mucus that is normally thick and impervious to sperm and ascending infections. High estrogen levels at midcycle change the characteristics of this mucus, and it becomes thin and stretchy. Estrogen-primed cervical mucus filters out nonsperm components of semen and forms channels that help direct sperm into the uterus (Fig. 19-9B). Midcycle mucus also creates a reservoir for sperm, allowing ongoing release during the next 24 to 72 hours and extending the potential time for fertilization (Katz, 1997).

FIGURE 19-9

A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

A. A ferning pattern is seen when periovulatory cervical mucus is spread and dried on a microscope slide. *(Courtesy of Dr. James C. Glenn.)* **B.** Examples of postcoital test slides. Slide 1: Columns within adequate cervical mucus help direct sperm into the uterine cavity. In patients with increasingly thick hostile mucus (slides 2 & 3), sperm display decreased motility.

Abnormalities in mucus production are most frequently observed in women who have undergone cryosurgery, cervical conization, or a loop electrosurgical excision procedure (LEEP) for treatment of an abnormal Pap smear. It has also been proposed that cervical infection can negatively impact mucus quality, however, the data in this area have been controversial. Implicated agents include *Chlamydia trachomatis* , *Neisseria gonorrhoeae* , *Ureaplasma urealyticum* , and *Mycoplasma hominis* (Cimino, 1993). Although there may be no advantage in terms of mucus quality, obtaining cultures for *C trachomatis* and *N gonorrhoeae* seems prudent to avoid causing ascending infection during HSG or intrauterine inseminations.

Postcoital Test

Also known as the Sims-Huhner test, this test can be performed to evaluate the presence of normal cervical mucus (Oei, 1995a, 1995b). A couple is requested to have intercourse on the day of ovulation. The woman is seen in the office within a few hours, and a sample of the cervical mucus is obtained from the cervical os with forceps or by aspiration. In the presence of high estrogen levels, mucus should be copious, stretchy, and relatively clear. Mucus should be able to be stretched to >5 cm. These qualities are summarized by the term *spinnbarkeit* . At least five motile sperm per high-power field should be visible under the microscope, although some authorities feel that a single, forward-moving sperm is adequate. There should be a minimal number of other cell types, such as inflammatory cells. When dried, the mucus should form a ferning pattern due to an increased salt concentration in the mucus prompted by increased preovulatory estrogen levels (Fig. 19-9A).

The most common reason for an abnormal test is improper timing. If mucus is scanty and thick, often termed *hostile* , then sperm

motility evaluation is futile, and the test should be repeated (Fig. 19-9B).

Despite the above discussion, the utility of the postcoital test is probably negligible in most circumstances. There is limited consensus on the definition of a normal test, and the predictive value for conception is poor (Oei, 1995b). Moreover, various approaches to improve an abnormal postcoital test have not convincingly increased pregnancy rates. In a prospective, randomized controlled trial, a normal postcoital test did not predict increased cumulative pregnancy rates (Oei, 1998).

Many infertility specialists recommend literally bypassing the cervix with intrauterine insemination in any woman with a history of cervical surgery, especially if she has noted a decrease in midcycle mucus production. The remaining utility of the postcoital test is for couples who will not consider intrauterine insemination or do not have intrauterine insemination readily available. It may also be useful in regions of the world in which more specific testing cannot be obtained, as a postcoital test will provide basic information regarding mucus production, appropriate intercourse practices, and presence of motile sperm.

Etiology of Infertility in the Male

Causes of male infertility can roughly be categorized as abnormalities of sperm production, abnormalities of sperm function, and obstruction of the ductal outflow tract.

NORMAL SPERMATOGENESIS

During evaluation of a male infertility patient, it is critical to understand the basics of male reproductive physiology. Analogous to the ovary, testes have two functions: the generation of mature germ cells (sperm) and the production of male hormones, primarily testosterone. The seminiferous tubules contain developing sperm and support cells called *Sertoli cells* or *sustentacular cells* (see Fig. 19-3C). The Sertoli cells form tight junctions that produce a blood-testis barrier. This avascular space within the seminiferous tubules protects sperm from antibodies and toxins, but also makes these cells dependent on diffusion for oxygen, nutrients, and metabolic precursors. Located between the seminiferous tubules are Leydig cells also called *interstitial cells* , which are responsible for steroid hormone production. In simplistic terms, Leydig cells are similar to the thecal cells of the ovary.

Unlike the ovary, testes contain stem cells that allow ongoing production of mature germ cells throughout a male's life. In a fertile male, approximately 100 to 200 million sperm are produced each day (Sigman, 1997). The process begins with a diploid (46,XY) spermatogonial cell, which grows and becomes a primary spermatocyte. The first meiotic division produces two secondary spermatocytes, and completion of meiosis results in four mature sperm with a haploid (23,X or 23,Y) karyotype (see Fig. 19-3C). During this developmental process, the majority of sperm cytoplasm is lost, mitochondria that provide energy are positioned in the midpiece of the sperm, and sperm develop flagella (see Fig. 19-3D).

Production of sperm requires approximately 70 days to complete. An additional 12 to 21 days is needed for sperm to be transported into the epididymis, where they further mature and develop motility (Heller, 1963; Hinrichsen, 1980; Rowley, 1970). It is important to realize that, due to this prolonged developmental period, the results of a semen analysis reflect events over the past 3 months, not a single point in time.

To fertilize an oocyte, human sperm must undergo a process known as *capacitation* . Capacitation results in sperm hyperactivation (an extreme increase in movement) as well as the ability of sperm to release acrosomal contents, which allow penetration of the zona pellucida.

Normal spermatogenesis is dependent on high local levels of testosterone. Luteinizing hormone (LH) from the anterior pituitary gland stimulates production of testosterone by the Leydig cells in the interstitium of the testes. Follicle-stimulating hormone (FSH) increases LH receptors on the Leydig cells, indirectly contributing to testosterone production. In addition, FSH increases production of sex hormone-binding globulin, also called androgen-binding protein. Androgen-binding protein binds testosterone and maintains high concentrations of this hormone in the seminiferous tubules (Sigman, 1997).

In addition to hormone levels, testicular volume often reflects spermatogenesis, and a normal volume is between 15 and 25 mL. The majority of this volume is provided by the seminiferous tubules, and therefore decreased testicular volume is a strong indicator of abnormal spermatogenesis.

Spermatogenesis is directed by genes on the Y chromosome with important contributions by autosomal genes, which have just

recently been elucidated. Therefore, genetic abnormalities may also adversely affect this process, as will be discussed later in this chapter.

Male fertility likely decreases modestly with age. A number of studies have demonstrated that pregnancy rates decrease and time to conception increases as male age increases. Studies of semen parameters across age have suggested that sperm concentration is maintained, however, sperm motility and morphology progressively worsen (Levitas, 2007). The clinical significance of this change is unclear (Kidd, 2001). In short, although advancing male age may have an impact on fertility, it is probably insignificant compared with the changes in women.

SEMEN ANALYSIS

Semen analysis is a core test in evaluation of male fertility status. For this test, the male is asked to refrain from ejaculation for 2 to 3 days, and a specimen is collected by masturbation into a sterile cup. If masturbation is not an option, then a couple can use specially designed Silastic condoms without lubricants. It is critical that the sample arrives in the laboratory within an hour of ejaculation to allow for optimal analysis.

The sample undergoes liquefaction, or thinning of the seminal fluid, due to enzymatic action from the liquid contribution of the prostate gland. This process takes 5 to 20 minutes and allows more accurate evaluation of the sperm contained in the seminal fluid. Ideally, two semen samples separated by at least a month should be analyzed. In practice, frequently only a single sample is analyzed if parameters are normal.

The reference values for the semen analysis are shown in Table 19-6 (World Health Organization, 1999). A clinician should remember a number of critical aspects with regard to this test. First, semen characteristics will vary across time in a single individual. Second, semen analysis results, particularly morphologic interpretation, will differ between laboratories. Therefore, reference ranges for the laboratory being used should be known. Note that the concept of "reference" range is more appropriate than "normal" range. Although total motile sperm count correlates with fertility, not all males with "normal" semen parameters display normal fertility (Guzick, 2001). The lack of absolute predictive value for this test is likely due to the fact that it does not provide information about sperm function, that is, the ultimate ability to fertilize an oocyte.

Table 19-6 Semen Analysis

Volume	>1.5 mL[a]
Count	>20 million/mL[a]
Motility	>50%[a]
Morphology	>30%[b]
	>14%[a] (Kruger's)[c]
WBCs	<1 million/mL[a]
Round cells	<5 million/mL[a]

WBCs = white blood cells.

[a] From World Health Organization, 1999, with permission.

[b] From World Health Organization, 1992, with permission.

[c] From Kruger, 1988, with permission.

Most semen analysis reports will indicate semen volume, pH, and presence or absence of fructose. Nearly 80 percent of semen volume comes from the seminal vesicles. The seminal fluid is alkaline and is thought to protect sperm from acidity present in prostatic secretions and in the vagina. Seminal fluid also provides fructose as an energy source for sperm. An acidic pH or lack of

fructose is consistent with obstruction of the efferent ductal system (Daudin, 2000).

Semen Volume

Low semen volume is often simply due to incomplete specimen collection or short abstinence interval. However, it may indicate partial obstruction of the vas deferens or retrograde ejaculation. Retrograde ejaculation follows failed closure of the bladder neck during ejaculation, allowing the seminal fluid to flow backwards into the bladder. Retrograde ejaculation should be suspected in men with diabetes mellitus, spinal cord damage, or a history of prostate or other retroperitoneal surgery, which may have produced nerve damage (Hershlag, 1991). Medications, particularly β-blockers, may contribute to this problem. A postejaculatory urinalysis can detect the presence of sperm in the bladder and confirm the diagnosis. If urine is properly alkalinized, these sperm are viable and can be retrieved to achieve pregnancy.

Sperm Count

A male partner may have normal sperm counts, *oligospermia* (low counts), or *azoospermia* (no sperm) (Jarow, 1989; Sharlip, 2002). Oligospermia is defined as a concentration of less than 20 million sperm per milliliter, with counts of less than 5 million per milliliter considered to be severe. The prevalence of azoospermia is approximately 1 percent of all men. Azoospermia may be due to obstruction in the outflow tract, termed obstructive azoospermia, such as that which occurs with absence of the vas deferens or severe infection. Azoospermia may also follow testicular failure (nonobstructive azoospermia). In the latter case, careful centrifugation and analysis may identify the presence of a small number of motile sperm adequate for use in IVF. Alternatively, this latter group may have viable sperm obtainable through either epididymal aspiration or testicular biopsy. Endocrine and genetic evaluation is indicated for men with abnormal sperm counts, as will be described later in this chapter.

Sperm Motility

Decreased sperm motility is termed *asthenospermia* . Some laboratories will distinguish between rapid (grade 3 to 4), slow (grade 2), and nonprogressive (grade 0 to 1) movement. Total progressive motility is the percentage of sperm exhibiting forward movement (grades 2 to 4). Asthenospermia has been attributed to prolonged abstinence, presence of antisperm antibodies, genital tract infections, or varicocele.

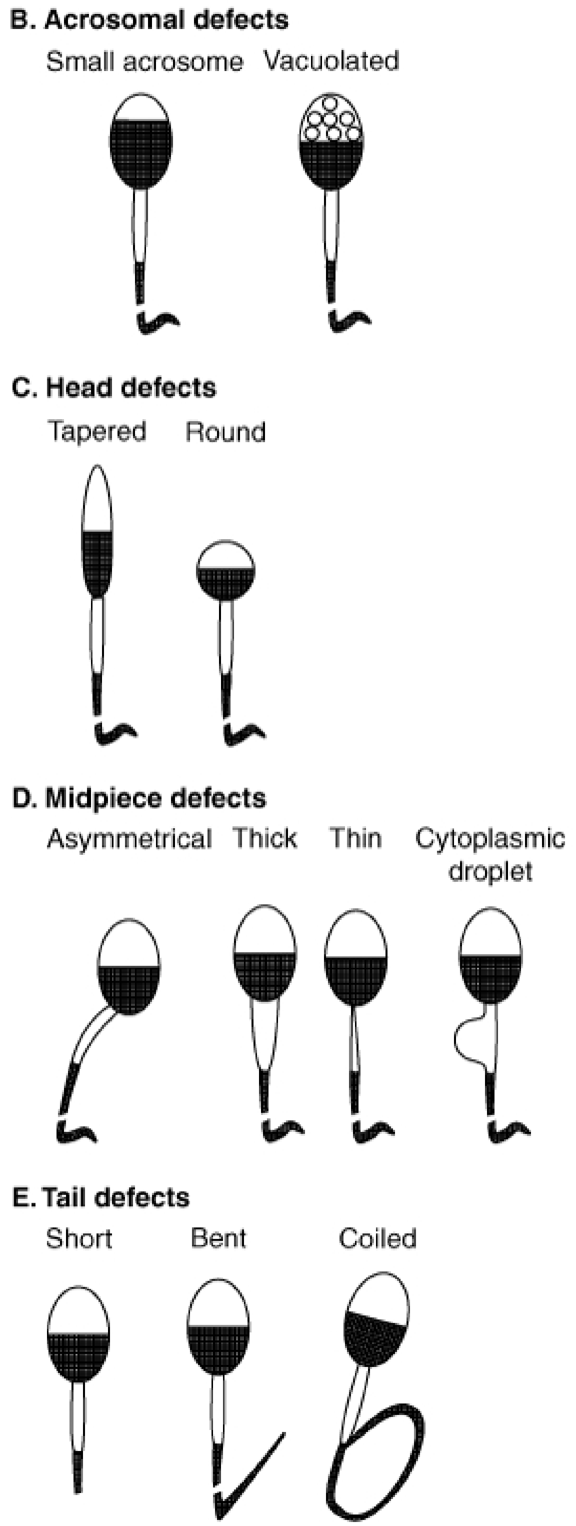
The hypo-osmotic swelling test can help to differentiate between dead and nonmotile sperm. Unlike dead sperm, living sperm can maintain an osmotic gradient. Thus, when mixed with a hypo-osmotic solution, living, nonmotile sperm with normal membrane function swell and coil as fluid is absorbed (Casper, 1996). Once identified, these viable sperm may be used for intracytoplasmic sperm injection.

Sperm Morphology

Abnormal sperm morphology is termed *teratospermia* . Many laboratories use the original classification in which normal morphology is characterized by over 50 percent of sperm exhibiting normal shape. More recently, Kruger and colleagues (1988) have developed strict criteria for defining normal morphology. Their studies defined a more detailed characterization of normal sperm morphology, with improved correlation with fertilization rates during IVF cycles. Their criteria require careful analysis of the shape and size of the sperm head, the relative size of the acrosome in proportion to the head, and characteristics of the tail, including length, coiling, or the presence of two tails (Fig. 19-10). Fertilization rates are highest with normal morphology greater than 14 percent. Significantly decreased fertilization rates are seen when normal morphology falls to less than 4 percent.

FIGURE 19-10

A. Normal sperm



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Some types of abnormally formed spermatozoa. **A.** Normal sperm. **B.** Acrosomal defects. **C.** Head defects. **D.** Midpiece defects. **E.** Tail defects.

Round cells in the sperm sample may represent either leukocytes or immature sperm. White blood cells (WBCs) can be

distinguished from immature sperm using a variety of techniques, including a myeloperoxidase stain for WBCs (Wolff, 1995). True leukocytospermia is defined as the presence of greater than one million WBCs per milliliter and may indicate the presence of chronic epididymitis or prostatitis. In this scenario, many andrologists would consider empiric antibiotic treatment prior to obtaining a repeat semen analysis. A common protocol would include doxycycline at a dosage of 100 mg orally twice daily for 2 weeks. Alternative approaches include culture of any expressible discharge or of the semen sample.

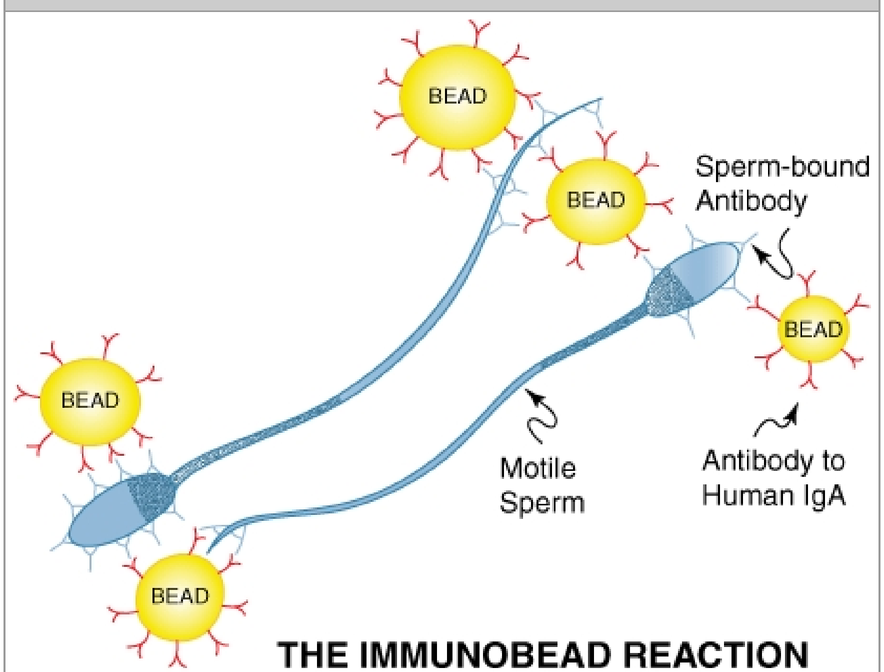
Unless a general obstetrician-gynecologist has developed a particular interest and expertise in the area of infertility, repeated abnormal semen analyses are an indication for referral to an infertility specialist. Although a referral may be made directly to a urologist, it may be more reasonable to have a couple be seen by a reproductive endocrinologist, as the female will also require evaluation. Treatment is likely to be more complex in these couples and will typically be directed to both partners. The reproductive specialist can determine the need for further referral of the male partner to a urologist for investigation of genetic, anatomic, hormonal, or infectious abnormalities.

ANTISPERM ANTIBODIES

Although antisperm antibodies may be detected in as many as 10 percent of men, controversy exists over the impact on fertility of antisperm antibodies (ASAs) in semen. These antibodies may be particularly prevalent following vasectomy, testicular torsion, testicular biopsy, or other clinical situations in which the blood-testis barrier is breached (Turek, 1994). It is currently felt that only IgG or IgA bound to the sperm head or midpiece are critical for decreasing fertilization capacity.

The most commonly employed assay contains immunobeads which are mixed with the sperm preparation. These beads will bind to antibodies present in a sperm sample. This mixture can be visualized under a standard microscope to look for beads binding to sperm (Fig. 19-11). Treatment historically included corticosteroids, but it is unclear that this approach improves fertility. Moreover, significant side effects, including aseptic necrosis of the hip, have been reported in treated patients.

FIGURE 19-11



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Immunoreactive beads bind to sperm carrying antibodies.

Current data suggest that antisperm antibodies do not need to be tested routinely as part of an infertility evaluation unless the

male partner has a clear risk factor for the presence of these antibodies. An exception would be those patients who will undergo IVF. Fertilization rates have been shown to be improved using intracytoplasmic sperm injection (ICSI) in an antibody-positive population.

ASSAYS OF SPERM FUNCTION

A wide variety of assays to test sperm function have been developed during the past few decades. The predictive significance of these assays is questionable, as they are based on highly nonphysiologic conditions, and results vary widely from infertility center to infertility center. Most are no longer used or are used only intermittently by infertility specialists. These tests are briefly described to provide more complete information to the general practitioner, however, they should not be considered part of a basic infertility evaluation.

Mannose Fluorescence Assay

The ability of sperm to recognize the zona pellucida of an oocyte is dependent on the presence of a number of proteins and sugars on the zona surface, including the sugar mannose. Acrosomal mannose-ligand receptor activity has been shown to correlate with IVF pregnancy rates (Benoff, 1993).

For this receptor assay, mannose residues in bovine serum albumin are modified so that they release fluorescence. A capacitated sperm sample from a patient is mixed with this fluorescent preparation. In a parallel experiment, sperm from a known fertile donor is mixed with the same fluorescent preparation in a separate dish. The patient's binding pattern is compared with the pattern obtained with the fertile male sample.

Hemizona Assay

The hemizona assay is a technique for analyzing the ability of a sperm sample to bind to the zona pellucida. Human oocytes are bisected (to prevent fertilization) and are mixed either with the partner's sperm or with fertile donor sperm. The hemizona index is calculated by dividing the number of patient sperm bound by the number of control sperm bound and multiplying by 100 (Burkman, 1988).

Sperm Penetration Assay

The sperm penetration assay is performed by mixing capacitated sperm with hamster oocytes. The zona pellucida typically prevents cross-species sperm binding and must first be removed from these test oocytes. The number of oocytes that are penetrated by sperm is calculated. The presumption is that more oocytes will be penetrated by sperm from fertile men than sperm from infertile men (Smith, 1987b).

Acrosomal Reaction

Penetration of an oocyte requires that sperm undergo an acrosomal reaction, during which the enzymatic contents of the acrosome are released on interaction with the oocyte membrane. Various methods can be used to induce the acrosomal reaction in a patient's sperm sample. The percentage of sperm which undergo the reaction is compared with that of a control sample (Sigman, 1997).

HORMONAL EVALUATION OF THE MALE

Hormonal testing in the male is analogous to endocrine testing in an anovulatory female (see Table 16-7). Essentially, abnormalities may be due to central defects in hypothalamic-pituitary function or to defects within the testes. Most urologists will defer testing unless a sperm concentration is less than 10 million/mL. Testing will include measurements of serum FSH and testosterone (T) levels. Elevated FSH and low T levels providing evidence of testicular failure. Alternatively, low FSH and low T levels are consistent with hypothalamic dysfunction, such as idiopathic hypogonadotropic hypogonadism or Kallman syndrome.

Unfortunately, most men with oligospermia will be found to have varying degrees of irreversible primary testicular failure. Nevertheless, it is important to determine whether testosterone replacement is indicated in this patient population. Normal spermatogenesis requires high levels of intratesticular testosterone, which cannot be achieved with exogenous testosterone. Furthermore, many of these men will lack spermatogonial stem cells. Therefore, testosterone replacement will not rescue sperm production. However, replacement will provide other benefits, such as improved libido and sexual function, and maintenance of muscle mass and bone density, as well as a general sense of well-being.

Additional hormonal testing may be included as part of an evaluation of the infertile male. Elevated serum prolactin levels and thyroid dysfunction impact spermatogenesis and are the most likely endocrinopathies to be detected (Sharlip, 2002; Sigman, 1997).

GENETIC TESTING OF THE MALE

Genetic abnormalities are a relatively common cause of abnormal semen characteristics. Approximately 15 percent of azoospermic men and 5 percent of severely oligospermic men will have an abnormal karyotype. Although genetic abnormalities cannot be corrected, they may have implications for the health of the patient or their offspring, and therefore should be pursued when indicated by poor semen analysis results.

Karyotype testing should be obtained on all azoospermic and severely oligospermic men. The lower limit in sperm concentration that prompts karyotype testing varies between practitioners, but lies between 3 and 10 million sperm per milliliter.

Klinefelter syndrome (47,XXY) will be a frequent finding. Klinefelter syndrome is observed in about 1 in 500 men in the general population and accounts for 1 to 2 percent of male infertility. Classically, these men are tall, undervirilized, and have gynecomastia and small, firm testes (De Braekeleer, 1991). As the phenotype varies widely, lack of these characteristics should not preclude chromosomal evaluation. Conversely, a clinician should strongly consider obtaining karyotype testing in any male with these characteristics. Autosomal abnormalities will also be found in a subset of men with severe oligospermia.

A patient with severely decreased sperm counts and a normal karyotype should be offered testing for microdeletion of the Y chromosome. Up to 15 percent of men with severe oligospermia or azoospermia will have small deletions in the region of the Y chromosome, termed the *azoospermia factor region* (AZF). If the deletion is within the AZFa or AZFb subregions, then it is unlikely that viable sperm can be recovered for use in IVF. Most men with an AZFc deletion will have viable sperm at biopsy. However, these deletions should be presumed to be inherited by their offspring. The clinical significance of microdeletions in the recently identified AZFd region is unknown, as these patients have apparently normal spermatogenesis (Kent-First, 1999; Pryor, 1997).

Patients may decline testing for microdeletion of the Y chromosome for a variety of reasons. Beyond infertility, there are no known health risks associated with these deletions. Many couples with azoospermia will chose to use donor sperm, and thus identification of this mutation may not be pertinent. Other couples reason that if the husband is able to have a child despite this deletion, there is no significant disadvantage if the abnormality is transmitted to any offspring.

Obstructive azoospermia may be due to congenital bilateral absence of the vas deferens (CBAVD). Approximately 70 to 85 percent of men with CBAVD will be found to have mutations in the cystic fibrosis transmembrane conductance regulator gene (*CFTR* gene), although not all will have clinical cystic fibrosis (Oates, 1994; Ratbi, 2007). Conversely, essentially all men with clinical cystic fibrosis will have CBAVD. Fortunately, testicular function in these men is usually normal, and adequate sperm may be obtained by epididymal aspiration to achieve pregnancy through IVF. Careful genetic counseling and testing the female partner for carrier status is critical in these situations.

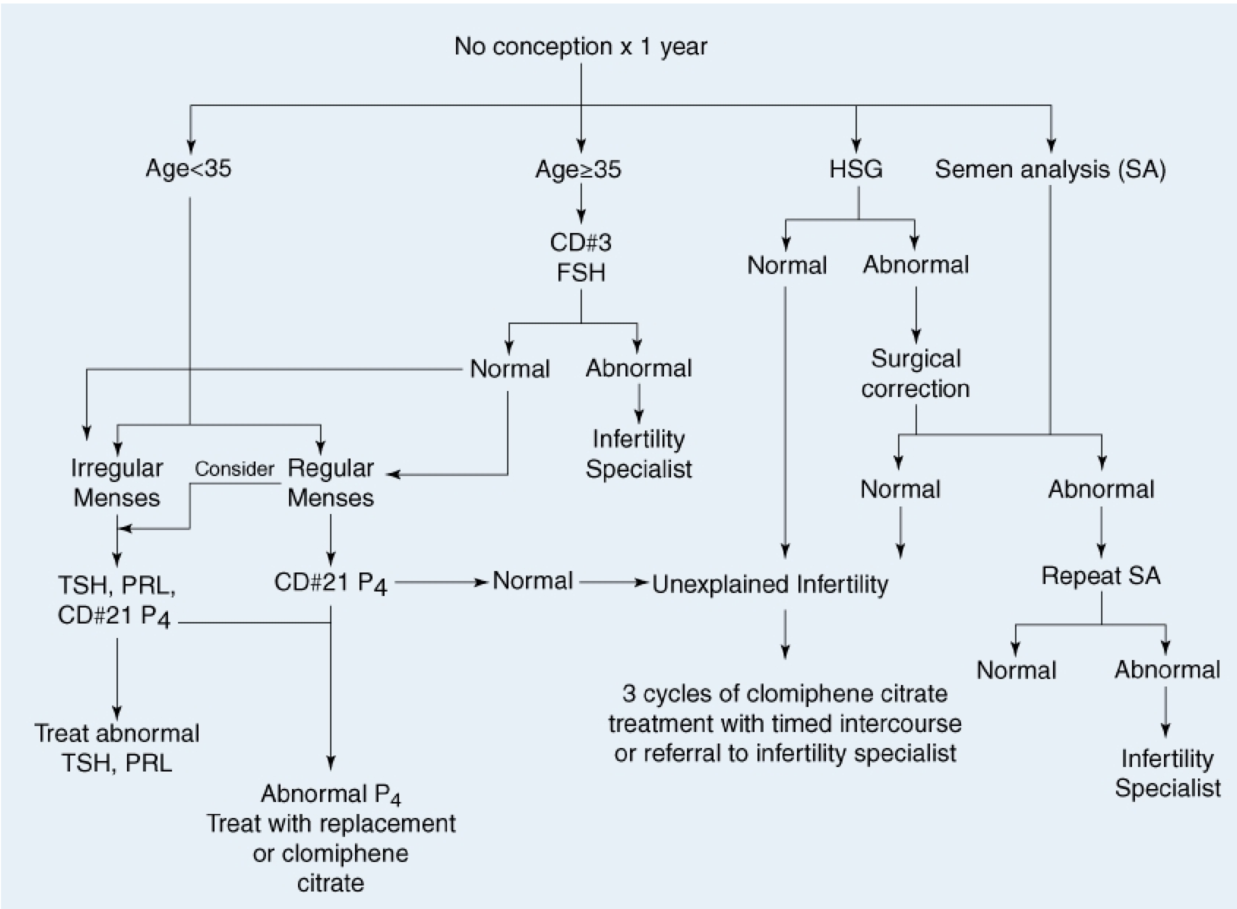
TESTICULAR BIOPSY

Evaluation of a severely oligospermic or azoospermic male may include either open or percutaneous testicular biopsy to determine whether viable sperm are present in the seminiferous tubules (Sharlip, 2002). For example, even men with testicular failure diagnosed by elevated serum FSH levels may have adequate sperm on biopsy for use in intracytoplasmic sperm injection. The biopsy specimen can be cryopreserved for future extraction of sperm during an IVF cycle. Thus, the biopsy may have diagnostic, prognostic, and therapeutic value.

CONCLUSION

Figure 19-12 provides an algorithm for the evaluation of an infertile couple. Details will vary between practitioners and will be affected by patient presentation. In general, the female partner should have some form of testing to confirm ovulation and should undergo hysterosalpingography, whereas the male partner should have semen analysis performed. In older women, it is crucial to evaluate an early follicular FSH level to ensure adequate follicular reserves. A subset of couples will decline hysterosalpingography and semen analysis if the woman has a clear ovulatory defect. These couples should be reminded that there is a relatively high incidence of couples having two abnormalities, one of which would be missed with this approach. These patients may be treated, but should be strongly encouraged to complete the evaluation if they do not conceive within a few months. Options for treatment are discussed in Chapter 20.

FIGURE 19-12



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Diagnostic algorithm for evaluation of the infertile couple. CD#3 = cycle day 3; CD#21 = cycle day 21; FSH = follicle-stimulating hormone; HSG = hysterosalpingography; P_4 = progesterone; PRL = prolactin; TSH = thyroid-stimulating hormone.

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TREATMENT OF THE INFERTILE COUPLE: INTRODUCTION

Infertility results from diseases of the reproductive system that impair the body's ability to perform basic reproduction function. Ten to 15 percent of the reproductive-aged population is infertile, and men and women are equally affected.

Infertility treatment is a complex process influenced by numerous factors. Important considerations include duration of infertility, a couple's age (especially the female's), and diagnosed cause. Additionally, the level of distress experienced by a couple should be taken into account.

In general, the first step involves identification of a primary cause and contributing factors, and treatment is aimed at their direct correction. Most are treated with conventional therapies such as medication or surgery. In many cases, therapy can begin without a complete evaluation, especially if a cause is obvious. However, if pregnancy does not quickly follow, then more thorough testing is required.

In contrast, it is common for evaluation not to yield a satisfactory explanation or to identify causes that are not amenable to direct correction. Recent advances in assisted reproduction have allowed for treatment of such cases. These approaches, however, are not without disadvantages. For example, appropriate treatments may pose ethical dilemmas for couples or their physician. Additionally, infertility treatment can be a financial burden, a significant source of emotional stress, or both.

An infertility specialist should not dictate treatment, but should offer and explain therapy options, which may include expectant management or even adoption.

LIFESTYLE THERAPIES

Environmental Factors

Increasing information suggests that some male and female infertility may result from environmental contaminants or toxins (Giudice, 2006). Exposures to endocrine-disrupting chemicals such as dioxins and polychlorinated biphenyls, agricultural pesticides and herbicides, phthalates (used in making plastics), and bisphenol A (used in the manufacture of polycarbonate plastic and resins) have been shown in wildlife and laboratory animals to be reproductive toxicants. These exposures may occur in utero, neonatally, or later.

Although direct links to infertility in humans are not conclusive, clinicians should counsel patients that environmental exposures to toxic substances should be avoided if possible. Currently, these cautions should be discussed carefully to avoid alarm.

Smoking

At least one-fifth of reproductive-aged men and women in the United States smoke cigarettes (Centers for Disease Control and Prevention, 2005) (Table 20-1). Several comprehensive reviews have summarized cumulative data on cigarette smoking and female fecundity, and all support the conclusion that smoking has an adverse impact (see Chap. 19, Social) (Practice Committee of the American Society of Reproductive Medicine, 2004c). Moreover, smoking's negative effects on female fecundity do not appear to be overcome by assisted reproductive technologies (ART). A 5-year prospective study of 221 couples found that the risk of failing to conceive with ART was more than doubled in smokers. Each year that a woman smoked was associated with a 9-percent increase in the risk of unsuccessful ART cycles (Klonoff-Cohen, 2001).

Table 20-1 Public Knowledge of the Risks of Smoking	
Smoking Risk	**Knowledge of Risk**
Lung cancer	99%
Respiratory	99%
Heart disease	96%
Miscarriage	39%
Osteoporosis	30%
Ectopic pregnancy	27%
Infertility	22%
Early menopause	17%

From American Society of Reproductive Medicine, 2004c, with permission.

The effect of smoking on male fertility is more difficult to discern. Male smokers often have comparatively reduced sperm concentrations and motility (Ramlau-Hansen, 2007). However, parameters often remain within the normal range.

Smoking is associated with an increased miscarriage rate in both natural and assisted conception cycles. The mechanism for this has not been elucidated, but the vasoconstrictive and antimetabolic properties of some components of cigarette smoke such as nicotine, carbon dioxide, and cyanide may lead to placental insufficiency. In addition, smoking in pregnant women is associated with an increased risk of trisomy 21 that results from maternal meiotic nondisjunction (Yang, 1999).

For these reasons, smoking should be discouraged for both male and female partners in couples with a history of infertility or recurrent miscarriage. When behavioral approaches fail, use of medical adjuncts such as nicotine replacement therapy or bupropion (Zyban, GlaxoSmithKline, Philadelphia, PA) may prove effective (see Table 1-20). Nicotine gum carries a category C classification, whereas the other preparations are designated as category D. The only non-nicotine Food and Drug Administration (FDA)-approved agent is bupropion, which carries a category B designation. Although studies of these agents in pregnant women have been limited, ideally pharmacologic smoking cessation therapies are best used prior to conception.

Alcohol

Alcohol consumption is widespread and increasing in many countries. Although it is well known that chronic alcohol abuse during pregnancy may lead to fetal alcohol syndrome, the impact on fertility has been less well studied (Homan, 2007). Retrospective investigations have generally found that moderate alcohol intake in women has no significant effect on fertility, whereas a high intake has been associated with reduced fecundability. However, one prospective study of Danish couples attempting pregnancy did demonstrate a decreased fecundability even among women with a weekly alcohol intake of five or fewer drinks (Jensen, 1998). This finding needs further corroboration, but it seems reasonable to encourage women to avoid alcohol when they are trying to become pregnant.

Caffeine

Caffeine is one of the most widely used pharmacologically active substances in the world. Recent studies have suggested that a positive dose-response relationship between caffeine and impaired fertility does exist. Hassan and Killick (2004) determined that women who consumed seven or more cups of coffee or tea per day were 1.5 times more likely to be subfertile. Significant caffeine consumption has also been linked to an increased abortion risk and is discussed again in Chapter 6, Caffeine. Accordingly, recommendations of caffeine intake moderation by infertile women seem prudent.

Weight Optimization

OBESE WOMEN

Ovarian function is dependent on weight. Low body fat content is associated with hypothalamic hypogonadism. In contrast, central body fat is associated with insulin resistance and contributes to ovarian dysfunction in many women with polycystic ovarian syndrome.

Lifestyle modification in overweight infertile women with PCOS leads to a reduction of central fat and improved insulin sensitivity, decreased hyperandrogenemia, lowered luteinizing hormone (LH) concentrations, and restoration of normal fertility in many cases (Kiddy, 1992; Hoeger, 2001). Even a 5- to 10-percent reduction in body weight has been shown to be successful in these women (Table 20-2) (Pasquali, 1989; Kiddy, 1992). Apart from diet, exercise can also improve insulin sensitivity. Weight loss and exercise are inexpensive and should be recommended as first-line management of anovulation in obese women with PCOS.

Table 20-2 Efficacy of Lifestyle Intervention in Anovulatory Infertile Women

Parameter	**Completed, *n* = 67 (Mean Â± SD or %)**	**Drop-Out, *n* = 20 (Mean Â± SD or %)**
BMI, basal	37.4 Â± 6.9	35.9 Â± 4.1
PCOS status	79%	72%
Anovulatory at baseline	81%	75%
Change in BMI	â€“3.7 Â± 1.6	â€“0.4 Â± 1.4[a]
Resumed spontaneous ovulation	90%	None
Pregnancies (cumulative: spontaneous or assisted reproductive technologies)	77%	None

The original cohort included 87 infertile obese women, most of whom had PCOS, and treatment consisted of a long-term lifestyle intervention program, including physical activity and hypocaloric diet. Those who completed were compared with those who dropped out.

[a] $p < .05$.

From Pasquali, 2006, with permission.

Although pharmacologic options can effectively treat anovulation if weight cannot be lost, it should also be noted that obesity is a significant risk factor for obstetric and perinatal complications. Therefore, strong consideration should be given to delaying treatments in morbidly obese women until their body mass index (BMI) can be reduced below 40 kg/m^2 . This is especially true if treatments involve surgery or risk of multifetal gestation.

UNDERWEIGHT WOMEN

Although obesity is more commonly encountered, undernutrition can also be a problem. The reproductive axis is closely linked to nutritional status and inhibitory pathways suppress ovulation in subjects with significant weight loss. Anorexia nervosa and bulimia nervosa affect up to 5 percent of reproductive-aged women and may cause amenorrhea and infertility (see Chap. 16, Eating Disorders). In those who do conceive, there is increased likelihood of miscarriage (Table 20-3). Fortunately, recovery may follow minimal acquisition of weight because energy balance has a more important effect than body fat mass.

Table 20-3 Relation of Comorbid Mental Disorders to Amenorrhea at Baseline and 10- to 15-Year Follow-Up among 173 Women with Bulimia Nervosa												
	Current Amenorrhea						Amenorrhea Over 10- to 15-Year Follow-Up					
	Total	Rate		Analysis			Total	Rate		Analysis		
Lifetime Mental Disorder	*n*	*n*	%	X^2	df	*p*	*n*	*n*	%	X^2	df	*p*
Anorexia nervosa				7.89	2	<.02				43.48	2	<.001
Present	59	16	27.1				50	43	86.0			
Subthreshold	23	4	17.1				19	9	47.4			
Absent	78	7	9.0				74	19	25.7			
Mood disorder				9.97	1	<.03				3.46	1	<.07
Present	104	10	9.6				92	51	55.4			
Absent	55	16	29.1				51	20	39.2			
Anxiety disorder				2.04	1	<.16				0.18	1	<.68
Present	48	5	10.4				42	22	52.4			
Absent	112	22	19.6				101	49	48.5			

From Crow, 2002, with permission.

Exercise

Physical activity has been demonstrated to have numerous health benefits. The relationship between exercise and fertility, however, is not straightforward. Competitive female athletes often experience amenorrhea, irregular cycles or luteal dysfunction, and infertility (see Chap. 16, Exercise-Induced Amenorrhea). This may be related not specifically to physical activity itself, but rather to low body fat content or physical stress associated with competition.

At this time, insufficient data exist to support or discourage physical activity in infertile women in the absence of documented ovarian dysfunction associated with low body weight.

Nutrition

In the absence of obesity or significant undernutrition, the role of diet in infertility is unclear. High-protein diets and gluten intolerance have been investigated as underlying causes in women (Meloni, 1999). In men, dietary antioxidants have been proposed as a potential way to improve male reproductive outcomes by reducing oxidative damage in sperm DNA. Additionally, the nutritional supplement, carnitine, had been often touted as having potential benefit for male infertility. This finding has not been confirmed by randomized, prospective trial (Sigman, 2006).

Despite a lack of conclusive benefits to nutritional supplements or diet modification in infertile couples, it does seem reasonable to recommend daily multivitamin supplementation to both. Folic acid is contained in most multivitamins, and daily doses of 400 μg orally are recommended for women attempting pregnancy to reduce the incidence of neural-tube defects in their fetuses (American College of Obstetricians and Gynecologists, 2003)

Stress Management

Stress has been implicated in reproductive failure. Although severe stress can result in anovulation, less significant stress may also play a role, but a mechanism has yet to be defined. Patients with higher stress levels have been found to have lower pregnancy rates when undergoing in vitro fertilization (IVF) treatments (Thiering, 1993). Consideration should be given to screening all infertile couples for evidence of anxiety or depression. Although pharmacologic management of stress is not typically recommended during infertility treatments, a "mind/body" approach that combines psychological counseling and meditation may be considered for those patients manifesting high levels of anxiety (Domar, 1990).

CORRECTION OF AN IDENTIFIED CAUSE

Correction of Ovarian Dysfunction

HYPERPROLACTINEMIA

Prolactin is a pituitary hormone that plays an important role in a variety of reproductive functions, and elevated levels are commonly encountered in clinical endocrinology (see Chap. 15, Hyperprolactinemia). If hyperprolactinemia is found, then physiologic, pharmacologic, or other secondary causes of hormone hypersecretion should be sought (see Table 12-3). In the absence of hypothyroidism or a pharmacologic cause of hyperprolactinemia, imaging studies should be performed to identify microadenoma or macroadenoma of the pituitary gland.

Dopamine agonists are the primary treatment of hyperprolactinemia (see Chap. 15, Treatment of Pituitary Adenomas). Surgical therapies should only be considered with prolactin-secreting adenomas resistant to medical therapy. If hyperprolactinemia is not associated with a pituitary lesion or if a lesion is less than 10 mm (microadenoma), then dopamine-agonist therapy is stopped during pregnancy. In these women, the risk of tumor expansion is low (Molitch, 1999). If the tumor size is 10 mm or larger (macroadenoma), then bromocriptine (Parlodel, Novartis Pharmaceuticals, East Hanover, NJ) use is advised during pregnancy to avoid significant tumor growth.

HYPOTHYROIDISM

Thyroid disorders are prevalent in reproductive-aged individuals and affect women four to five times more frequently than men. Clinical hypothyroidism is associated with changes in cycle length and amount of bleeding. Specifically, oligomenorrhea and amenorrhea are frequent findings. Although ovulation and conception can still occur in those with mild hypothyroidism, treatment with thyroxine usually restores a normal menstrual pattern and enhances fertility.

Subclinical hypothyroidism may also be associated with ovarian dysfunction (Strickland, 1990). Lincoln and colleagues (1999) found a 2-percent incidence of elevated thyroid-stimulating hormone (TSH) levels in 704 asymptomatic women seeking evaluation for infertility. Correction of hypothyroidism in those with ovarian dysfunction and elevated TSH levels led to pregnancy in 64 percent of patients. Although there is a possible effect on fertility, the effects of subclinical hypothyroidism on pregnancy outcomes is unclear. Therefore, early detection and treatment of hypothyroidism of any degree in women seeking treatment for infertility is advised.

OVULATION INDUCTION

Ovarian dysfunction is the most common indication for the use of medications to induce ovulation. These agents can also be used in ovulatory women to increase the likelihood of pregnancy in couples with other causes of infertility or unexplained infertility. Use of these medications in this manner has been referred to as superovulation (SO), ovulation enhancement, or controlled ovarian hyperstimulation (COH). In contrast, we prefer the term *"ovulation induction"* to describe treatment with medications to stimulate normal ovulation in women with ovarian dysfunction.

Frequent causes of ovarian dysfunction include PCOS and diminished ovarian reserve. Less often, central (hypothalamic or pituitary) disorders or thyroid dysfunction can result in infertility. Rarely, ovarian tumors or adrenal abnormalities lead to abnormal ovarian function. Treatment of ovarian dysfunction should be based on the identified cause as well as the results of any prior attempted treatments.

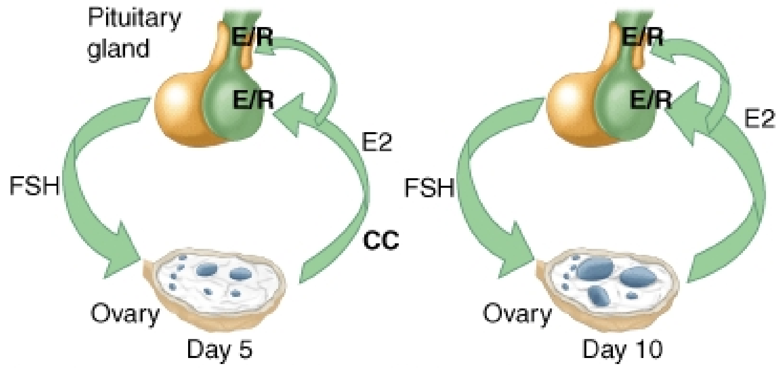
CLOMIPHENE CITRATE

Pharmacologic Effects

Clomiphene citrate (CC) is the initial treatment for most anovulatory infertile women. Chemically similar to tamoxifen, CC is a nonsteroidal triphenylethylene derivative that demonstrates both estrogen agonist and antagonist properties. Antagonist properties predominate except at very low estrogen levels. As a result, negative feedback that is normally produced by estrogen in the hypothalamus is reduced (Fig. 20-1). Gonadotropin-releasing hormone (GnRH) secretion is improved and stimulates pituitary gonadotropin release. The resulting increase in follicle-stimulating hormone (FSH), in turn, drives ovarian follicular activity.

FIGURE 20-1

Clomiphene Citrate Treatment



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Effect of clomiphene citrate (**CC**) administration. Administration leads to estrogen receptor (**ER**) depletion at the level of the pituitary and mediobasal hypothalamus. As a result, estrogen-negative feedback is interrupted centrally and follicle-stimulating hormone (**FSH**) secretion increases from the anterior pituitary, leading to maturation of multiple follicles. By the late follicular phase, because of clomiphene citrate's long retention within tissues, ER depletion continues centrally. As a result, increased estradiol (**E2**) secretion from the ovary is not capable of normal negative feedback on FSH release. This leads to a growth of multiple dominant follicles and multiple ovulations. *(Redrawn from Casper, 2003, with permission.)*

Tamoxifen has also been used successfully for ovulation induction. However, it is not approved by the FDA for this indication and has not been demonstrated to have significant advantage compared with CC.

Administration

Clomiphene citrate is administered orally, typically starting on the third to fifth day after the onset of spontaneous or progestin-induced menses. Ovulation rates, conception rates, and pregnancy outcome are similar regardless of whether treatment begins on cycle day 2, 3, 4, or 5. Prior to therapy, sonography is advised to exclude signs of significant spontaneous follicular maturation or residual follicular cysts. A pregnancy test is also indicated after spontaneous menses. Although, not a proven teratogen, CC is classified as category X by the FDA and thus, is contraindicated in suspected or documented pregnancy.

The dose required to achieve ovulation correlates with body weight, although there is no reliable way to accurately predict which dose will be required in an individual woman (Lobo, 1982). Consequently, CC is titrated empirically to establish the lowest effective dose for each individual patient. Treatment typically begins with a single 50-mg tablet daily for 5 consecutive days. Doses are increased by 50-mg increments in subsequent cycles until ovulation is induced. The dose of clomiphene citrate should not be increased if normal ovulation is confirmed, and lack of pregnancy alone does not justify an increase in dose.

The effective dose of CC ranges from 50 mg/d to 250 mg/d, although doses in excess of 100 mg/d are not approved by the FDA. Some studies have suggested that adjunctive therapy with glucocorticoids may benefit some patients not responsive to CC alone. This therapy may be empiric or individualized based on elevated dehydroepiandrosterone sulfate (DHEAS) levels.

In general, women failing to ovulate with 100 mg/d dosing or failing to conceive following 3 to 6 months of ovulatory response to CC should be considered candidates for alternative treatments. In a retrospective study including 428 women who received CC for ovulation induction, 84.5 percent of pregnancies achieved with treatment occurred during the first three ovulatory cycles (Gysler, 1982).

Insulin-Sensitizing Agents

Although PCOS appears to be a heterogeneous disorder, many women with this condition exhibit insulin resistance (see Chap. 17, Ovarian Hyperthecosis and HAIRAN Syndrome). Insulin resistance leads to compensatory hyperinsulinemia and dyslipidemia.

Given the strong evidence that hyperinsulinemia plays a pivotal pathogenic role in development of PCOS, it is reasonable to assume that interventions that reduce circulating insulin levels in women with PCOS may restore normal reproductive endocrine function. As discussed, weight loss, nutrition, and exercise have clearly led to reduced hyperinsulinemia with resolution of hyperandrogenism, and in some cases, resumption of ovulatory function in overweight women with PCOS. However, women may be poorly compliant, and weight loss is rarely maintained over time.

Recently, a new class of oral antidiabetic compounds, *insulin-sensitizing agents,* has been developed, which in early studies show promise in the treatment of PCOS. When administered to insulin-resistant patients, these compounds act to increase target tissue responsiveness to insulin, thereby reducing compensatory hyperinsulinemia (Antonucci, 1998). Current insulin-sensitizing agents include the biguanides and thiazolidinediones (see Chap. 17, Insulin-Sensitizing Agents).

Preliminary studies suggested that the biguanide, metformin (Glucophage, Bristol-Myers Squibb, New York, NY), 500 mg orally three times daily or 850 mg twice daily with meals, administered to women with PCOS increased the frequency of spontaneous ovulation, menstrual cyclicity, and ovulatory response to CC (Nestler, 1998; Palomba, 2005; Vandermolen, 2001). However, in contrast to those initial studies, a recent, large, prospective, randomized, multi-center trial does not support the hypothesis that metformin, either alone or in combination with CC, improves the rate of live birth in women with PCOS (Legro, 2007).

Gonadotropins

Clomiphene citrate is easy to use and leads to ovulation in the vast majority of patients, but pregnancy rates are disappointing (50 percent or less) (Hammond, 1983; Raj, 1977; Zarate, 1971). Lower-than-expected pregnancy rates with CC have been attributed to its long half-life and peripheral anti-estrogenic effects, mainly on the endometrium and cervical mucus. In such individuals, who are often classified as "clomiphene resistant", the next step is traditionally the administration of exogenous gonadotropin preparations via injections.

As with CC, the goal of ovulation induction with gonadotropins is simply to normalize ovarian function. Ideally, the dosage used should be the minimum required to cause normal development of a single dominant follicle. Because the response to gonadotropins can vary greatly from individual to individual and even from cycle to cycle, intensive monitoring is required to adjust dosage and timing of ovulation.

Gonadotropin preparations vary in terms of their source (urinary or recombinant) and the presence or absence of LH activity. Traditional urinary-derived human menopausal gonadotropin (hMG) preparations are extracted and purified from the urine of postmenopausal women, and their active components are both FSH and LH. The primary source of the LH activity is human chorionic gonadotropin (hCG), although significant LH is also present in the older, non-highly-purified hMG products (Filicori, 2002). Highly purified urinary preparations allow for administration via the subcutaneous route with minimal or no reaction at the injection site. Alternatives to hMG include highly purified urinary gonadotropin preparations and purified recombinant FSH (Table 20-4).

Table 20-4 Gonadotropin Preparations Used for Ovulation Induction					
Name	**Manufacturer**	**Product Type**	**FSH Activity**	**LH Activity**	**hCG Activity**
Bravelle	Ferring, Suffern, NY	Vial	Highly purified urinary	Minimal	Minimal
Fertinex[a]					
Follistim	Organon, Roseland, NJ	Pen or vial	Highly purified recombinant	None	None
Gonal-f	Serono, Rockland, MA				
Menopur	Ferring, Suffern, NY	Vial	Highly purified urinary	Minimal	Highly purified urinary
Repronex	Ferring, Suffern, NY	Vial	Urinary	Urinary	Urinary
Pergonal[a]					
Humagon[a]					

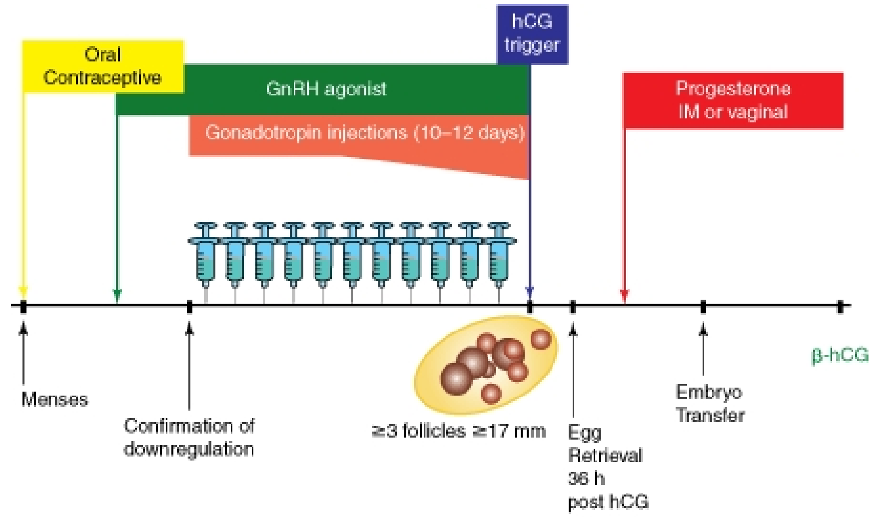
FSH = follicle-stimulating hormone; hCG = human chorionic gonadotropin; LH = luteinizing hormone.

[a] No longer available.

Both LH and FSH activity are required for normal ovarian steroidogenesis and follicular development. In many cases, pure FSH preparations can be used because of adequate endogenous LH production. However, for ovulation induction in patients with hypogonadotropic amenorrhea, LH activity must be provided from an exogenous source. Options include hMG, recombinant LH, and low-dose (diluted) urinary or recombinant hCG. Ovulation induction in women with PCOS can be performed either with FSH-only containing products or those containing both LH and FSH activity. At present, data do not support the superiority of one preparation over another.

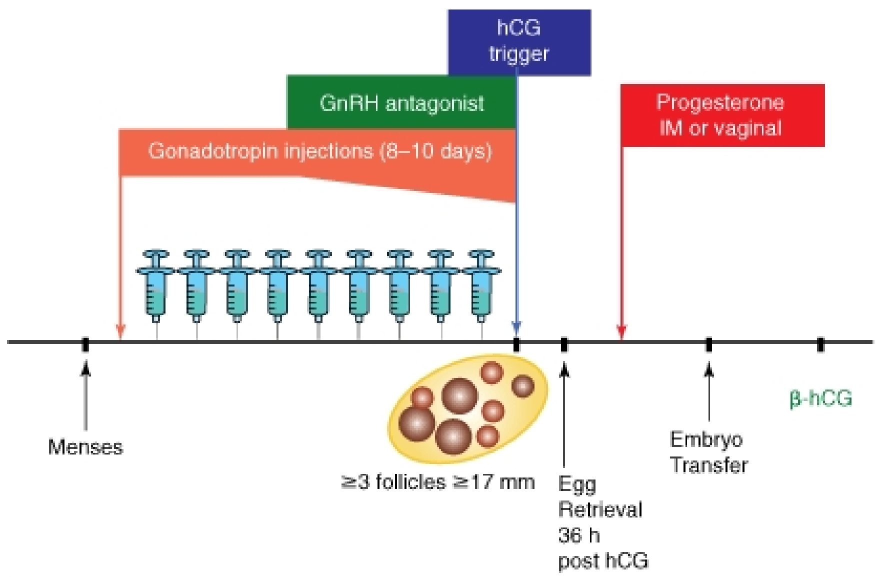
Most clinicians begin ovulation induction attempts at a low dosage (50 to 75 IU/d) of gonadotropins and gradually increase the dose if no ovarian response (as assessed by serum estradiol measurements) is noted after several days (Fig. 20-2). This is referred to as a "step-up" protocol (Fig. 20-3). A "step-down" protocol can also be used with the advantage of a decreased duration of stimulation. However, the risk of excessive ovarian response, such as development of multiple follicles or ovarian hyperstimulation syndrome, may be increased with this approach. With either approach, if a patient fails to conceive, subsequent cycles may be started at higher dosages based on prior response.

FIGURE 20-2



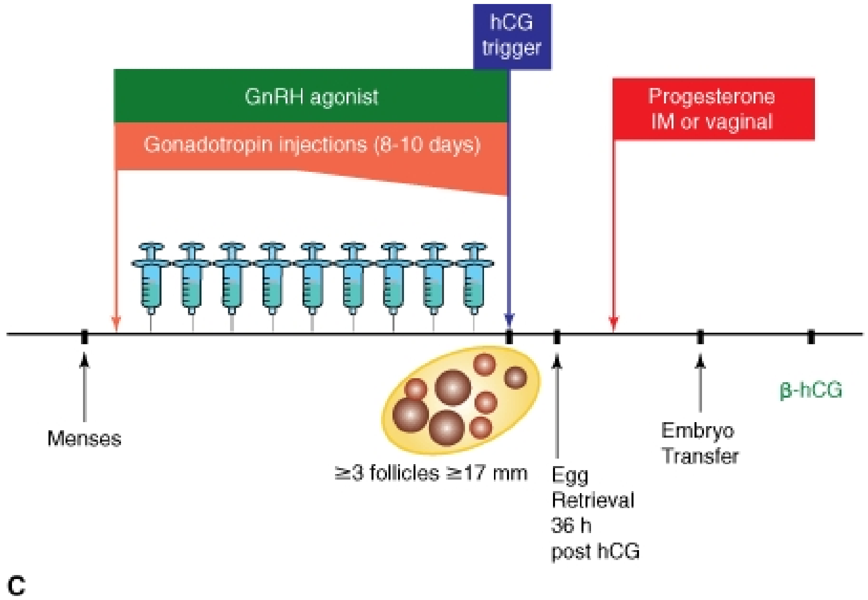
A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



B

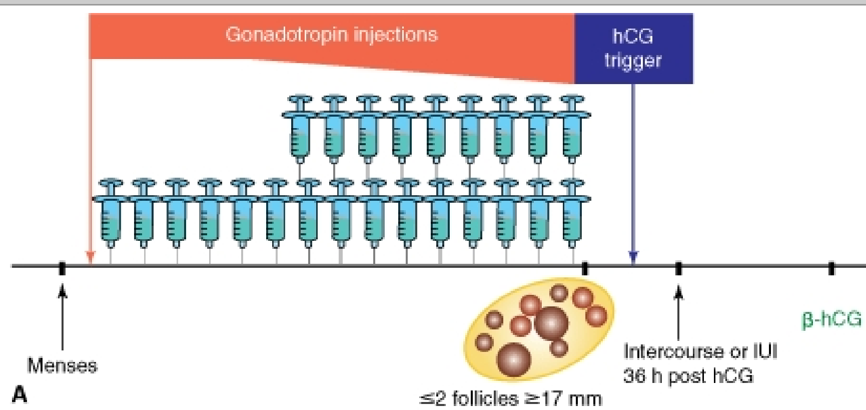
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



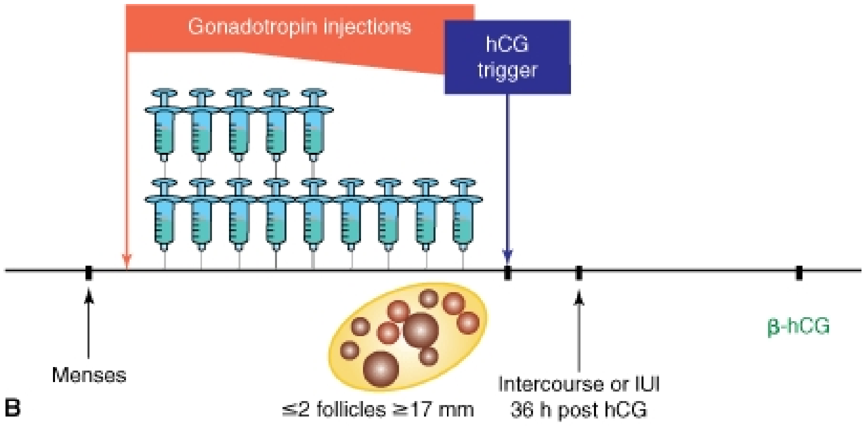
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Drug protocols for ovulation induction. **A.** Combination oral contraceptive pretreatment, downregulation gonadotropin-releasing hormone (GnRH) agonist cycle protocol. **B.** GnRH antagonist cycle protocol. **C.** GnRH agonist flare cycle protocol. hCG = human chorionic gonadotropin; IM = intramuscular.

FIGURE 20-3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

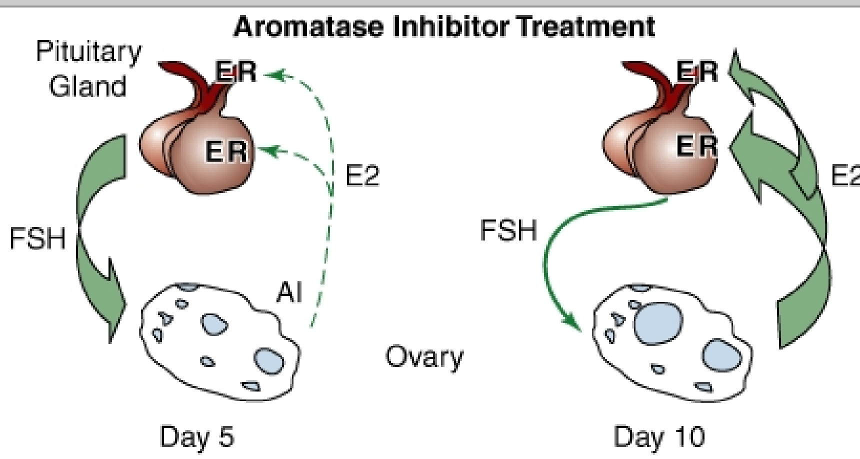
Ovulation induction protocols. **A.** Step-up protocol. **B.** Step-down protocol. hCG = human chorionic gonadotropin; IUI = intrauterine insemination.

In general, results of gonadotropin stimulation in women with PCOS are less successful than in patients with hypogonadotropic amenorrhea (Balen, 1994). Women with PCOS have ovaries that are highly sensitive to gonadotropin stimulation and have a higher risk of excessive ovarian response and multifetal pregnancy than those with normal ovaries (Farhi, 1996).

Aromatase Inhibitors

Gonadotropins are associated with more effective ovulation induction and higher pregnancy rates than CC, but are expensive and carry higher risks for ovarian hyperstimulation syndrome and multifetal gestation. Accordingly, aromatase inhibitors have been investigated as new ovulation-inducing agents (Fig. 20-4). These agents were originally developed for breast cancer treatment and effectively inhibit *aromatase,* a cytochrome P-450 hemoprotein that catalyzes the rate-limiting step in estrogen production. Aromatase inhibitors are orally administered, easy to use, and relatively inexpensive with minor side effects.

FIGURE 20-4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Effect of aromatase inhibitor (**AI**) administration. Administration suppresses ovarian estradiol (**E2**) secretion and reduces estrogen-negative feedback at the pituitary and mediobasal hypothalamus. Increased follicle-stimulating hormone (**FSH**) secretion from the anterior pituitary stimulates growth of multiple ovarian follicles. Later in the follicular phase, the effect of the aromatase inhibitor is reduced, and E2 levels increase as a result of follicular growth. Because aromatase inhibitors do not affect estrogen receptors (**ER**) centrally, the increased E2

levels result in normal negative feedback on FSH secretion. Follicles smaller than the dominant follicle undergo atresia, with resultant monofollicular ovulation in most cases. *(Redrawn from Casper, 2003, with permission.)*

The most widely used aromatase inhibitor to induce ovulation in anovulatory and ovulatory infertile women is letrozole (Femara, Novartis Pharmaceuticals, East Hanover, NJ). Compared with CC, its use is associated with a thicker endometrium and a trend toward higher pregnancy rates following ovulation induction. When used in combination with gonadotropins, letrozole leads to lower gonadotropin requirements and pregnancy rates comparable with gonadotropin treatment alone (Mitwally, 2004; Casper 2003). The typical dosage used is 2.5 to 5 mg orally daily for 5 days.

Data suggesting that letrozole use for infertility treatment might be associated with a higher risk of congenital cardiac and bone malformations in the newborn are contradictory (Biljan, 2005; Tulandi, 2006). However, in November 2005, the manufacturer issued a statement to physicians worldwide advising that letrozole use in premenopausal women, specifically its use for ovulation induction, is contraindicated. As a result, it is not likely that letrozole will gain widespread acceptance for ovulation induction in the near future. Well-designed randomized prospective trials confirming safety are needed.

A second aromatase inhibitor, anastrozole, is of the same compound class as letrozole and has also been approved for treatment of women with breast cancer. Only a few randomized studies have been completed evaluating this agent for ovulation induction (Al-Omari, 2004; Sipes, 2006). At this time, no concerns have been raised regarding its teratogenicity (Casper, 2007). Experience with anastrozole (Arimidex, AstraZeneca, Wilmington, DE) in ovulation induction at this time is limited, however. Ideal dosage requirements are currently unknown.

COMPLICATIONS OF FERTILITY DRUGS

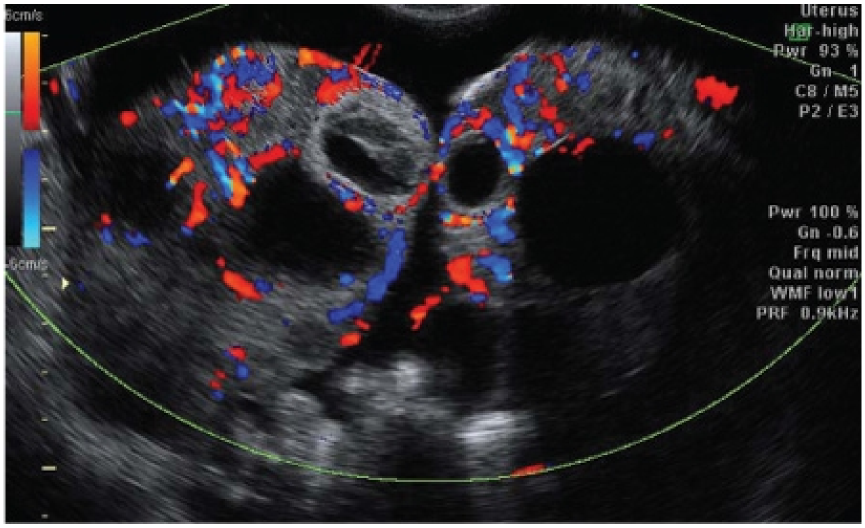
Ovarian Hyperstimulation Syndrome

Ovarian hyperstimulation syndrome (OHSS) is a clinical symptom complex associated with ovarian enlargement resulting from exogenous gonadotropin therapy (Fig. 20-5). Symptoms may include abdominal pain and distension, ascites, gastrointestinal problems, respiratory compromise, oliguria, hemoconcentration, and thromboembolism. These symptoms may develop during ovulation induction or in early pregnancies that were conceived through exogenous ovarian stimulation.

FIGURE 20-5

A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

A. Transvaginal sonogram of ovaries with multiple large cysts secondary to ovarian hyperstimulation syndrome. Ovaries are enlarged and meet in the midline. Ascites surrounds these enlarged ovaries. **B.** Color Doppler transvaginal sonography is often performed to exclude torsion in these patients.

Pathophysiology

The etiology of OHSS is complex, but hCG, either exogenous or endogenous (derived from a resulting pregnancy), is believed to be an early contributing factor. Development of OHSS involves increased vascular permeability with loss of fluid, protein, and electrolytes into the peritoneal cavity, and leads to hemoconcentration. Increased capillary permeability is felt to result from vasoactive substances produced by the corpus luteum. Vascular endothelial growth factor (VEGF) is believed to play a major role, and angiotensin II may also be involved. Hypercoagulability may be related to hyperviscosity following hemoconcentration or may be secondary to the high estrogen levels present with a resulting increase in coagulation factors. Predisposing factors for OHSS include multifollicular ovaries such as with PCOS, young age, high estradiol levels, and pregnancy.

Diagnosis and Treatment

Abdominal pain is prominent and caused by ovarian enlargement together with accumulation of peritoneal fluid. Although sonographic examination of women with OHSS usually reveals enlarged ovaries with numerous follicular cysts and ascites, OHSS is a clinical diagnosis. Several different classification schemes have been proposed to categorize the severity of this syndrome (Table 20-5).

Table 20-5 Classification and Staging of Ovarian Hyperstimulation Syndrome
Grade 1: Abdominal distention/discomfort
Grade 2: Grade 1 plus nausea and vomiting or diarrhea Ovaries enlarged 5â€“12 cm
Grade 3: Sonographic evidence of ascites
Grade 4: Clinical evidence of ascites or hydrothorax or difficulty breathing
Grade 5: All of the above plus decreased blood volume, hemoconcentration, diminished renal perfusion and function, and coagulation abnormalities

From Whelan, 2000, with permission.

Treatment of OHSS is generally supportive. Paracentesis is typically performed transvaginally as an outpatient and can ameliorate abdominal discomfort and relieve respiratory distress. Re-accumulation of ascites may prompt additional paracenteses or rarely, placement of a percutaneous pigtail catheter. Untreated hypovolemia can lead to renal, hepatic, or pulmonary end-organ failure. Thus, fluid balance must be maintained by replacement with an isotonic fluid such as normal saline. Monitoring of electrolytes is critical. Because of hypercoagulability in these women, prophylaxis for thromboembolism should strongly be considered with severe OHSS (see Table 39-11).

Prevention

Strategies to avoid OHSS during exogenous ovulation induction include decreasing follicular stimulation (a decreased FSH dose), "coasting" (withholding FSH administration for one or more days prior to hCG injection), substitution of hCG for FSH during the final days of ovarian stimulation, and prophylactic treatment with volume expanders.

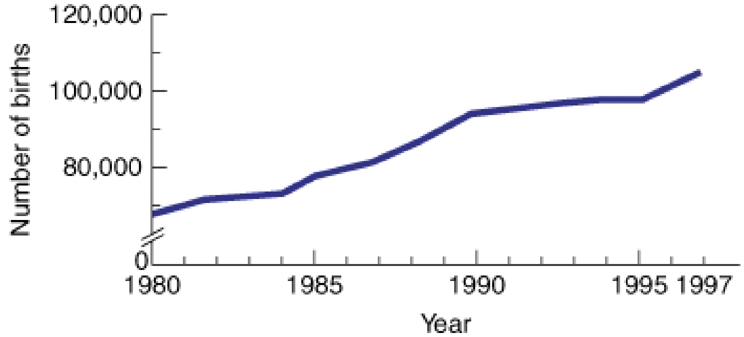
If concern of OHSS is present during induction, then the hCG trigger can be withheld, resulting in cycle cancellation. Alternatively, a single dose of a GnRH agonist such as leuprolide acetate (Lupron, TAP Pharmaceutical, Lake Forest, IL) can be used in place of hCG. This results in an endogenous LH surge, which can bring about the final stages of follicle and oocyte maturation without significant risk of OHSS. Prevention of pregnancy does not completely eliminate the risk of OHSS, but certainly serves to limit the duration of the symptoms. Thus, an additional option in ART cycles is to freeze all embryos and forgo embryo transfer that cycle.

Multifetal Gestation

Higher-order multifetal pregnancy is an adverse outcome of infertility treatment, and in general, increased fetal numbers lead to greater risk of perinatal and from maternal morbidity and mortality. In these cases, prematurity leads to most adverse events, but fetal growth restriction and discordance may also be factors.

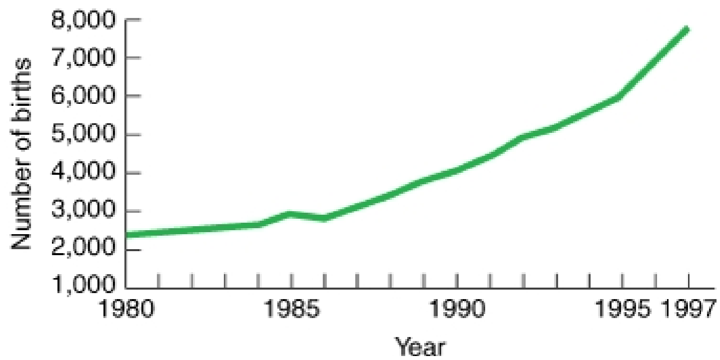
From 1980 through 1997, the number of twin births rose by slightly more than 50 percent, whereas the number of higher-order multifetal births increased by over 400 percent (Fig. 20-6) (Martin, 1999). In an analysis of recent data from the Society for Assisted Reproductive Technology (SART) and from the Centers for Disease Control and Prevention (CDC) National Center for Health Statistics (2000), the CDC has estimated that approximately 20 percent of triplets and higher-order multifetal births were attributable to spontaneous events; 40 percent were related to ovulation-inducing drugs without ART; and 40 percent resulted from ART. However, further analysis of the same data indicates that the overwhelming majority of all multifetal births results from spontaneously conceived twin gestations and that only approximately 10 percent result from IVF and related procedures.

FIGURE 20-6



A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



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Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Trends in frequency of multifetal gestation deliveries. **A.** Number of twin births in the United States from 1980 to 1997. **B.** Number of triplet and higher-order multifetal births in the U.S. for the same time period. *(From Martin, 1999, with permission.)*

That said, several issues in infertility care contribute to the increased incidence of higher-order multifetal pregnancies. An infertile couple's sense of urgency may lead to a preference for more aggressive strategies involving gonadotropin treatment or for more embryos to be transferred in IVF cycles. Clinicians may feel competitive pressures to achieve higher pregnancy rates and may be inclined to turn to superovulation (SO) or IVF earlier in treatment or to transfer a greater number of embryos.

Efforts to reduce multifetal gestation using serum estradiol limits and arbitrary sonographic criteria of follicular size in patients undergoing ovulation induction (OI) or SO have been ineffective (Gleicher, 2000). In a multicenter randomized clinical trial involving 1,255 OI cycles, hCG was withheld if the estradiol concentration rose above 3,000 pg/mL or more than six follicles greater than 18 millimeters in diameter were present (Guzick, 1999). Despite these limits on hCG administration, the multifetal gestation rate was still 30 percent. Although sonography and serum estradiol monitoring have not reduced the incidence of multifetal gestation and OHSS, the risk of multifetal pregnancy does correlate with the magnitude of follicular response as indicated by follicle number and serum estradiol levels. However, there is no consensus among centers regarding specific sonographic criteria or estradiol levels beyond which hCG should not be administered.

Patients with higher-order multifetal gestations are faced with options of continuing their pregnancy, with all the risks previously described; terminating the entire pregnancy; or electing multifetal pregnancy; reduction (MFPR). Reduction lowers the number of

fetuses to decrease the risk of maternal and perinatal morbidity and mortality. Although MFPR decreases risks associated with preterm delivery, it often creates profound ethical dilemmas. Moreover, multifetal reduction reduces, but does not eliminate, the risk of fetal growth restriction in remaining fetuses. With MFPR, pregnancy loss and prematurity are primary risks. However, current data suggest that such complications have decreased as experience with the procedure has grown (Evans, 2005).

OVARIAN DRILLING

Surgical ovarian wedge resection was the first established treatment for anovulatory PCOS patients. It was largely abandoned because of postsurgical adhesion formation, which converted endocrinologic subfertility to mechanical subfertility (Adashi, 1981; Buttram, 1975; Stein, 1939). As a result, it was replaced by medical ovulation induction with CC and gonadotropins (Franks, 1985). However, medical ovulation induction, as discussed earlier, has limitations. Accordingly, surgical therapy using laparoscopic techniques known as laparoscopic ovarian drilling (LOD) is an alternative in women resistant to medical therapies.

During LOD, electrosurgical coagulation, laser vaporization, or harmonic scalpel may be used to create multiple perforations in the ovarian surface and stroma (see Section 41-32, Ovarian Drilling). In many uncontrolled observational studies, drilling has led to a temporary high rate of spontaneous postoperative ovulation and conception, or to improved medical ovulation induction (Armar, 1990, Farhi, 1995; Greenblatt, 1987; Kovacs, 1991).

The mechanism of action with LOD is thought to be similar to that of ovarian wedge resection. Both procedures may destroy ovarian androgen-producing tissue and reduce peripheral conversion of androgens to estrogens. Specifically, a fall in serum levels of androgens and LH, and an increase in FSH levels have been demonstrated after ovarian drilling (Armar, 1990; Greenblatt, 1987). The endocrine changes following surgery are thought to convert the adverse androgen-dominant intrafollicular environment to an estrogenic one, and to restore the hormonal environment to normal by correcting disturbances of ovarian-pituitary feedback (see Chap. 17, Insulin Resistance). (Aakvaag, 1985; Balen, 1993). Thus, both local and systemic effects are thought to promote follicular recruitment and maturation and subsequent ovulation.

Risks of ovarian drilling include postoperative adhesion formation as well as the other risks of laparoscopic surgery (see Section 41-28, Laparoscopy). Additionally, theoretical risks of diminished ovarian reserve and premature ovarian failure remain to be well investigated. As surgery is more invasive, ovarian drilling is generally not offered prior to consideration of medical therapies.

Correction of Diminished Ovarian Reserve

Ovarian dysfunction may result from ovarian failure or from a diminished ovarian reserve, either of which may follow normal aging, disease, or surgical castration. Even if a woman is spontaneously menstruating, a basal (day 2 or 3) FSH level above 15 IU/L predicts that medical therapies including exogenous gonadotropins will be of little benefit. For these women, the option of using donor eggs should be considered. Expectant management may also be considered, although the likelihood of pregnancy is low.

Correction of Anatomic Abnormalities

Anatomic distortions of the female reproductive tract are a major cause of infertility and may prevent ovum entry into the fallopian tube; impair transport of ova, sperm, or embryos; or interfere with implantation. The three primary types of anatomic abnormalities include tubal factors, peritoneal factors, and uterine factors. Each has differing effects and therefore may require different therapies.

TUBAL FACTORS

Tubal occlusion can arise from congenital abnormality, infection, or iatrogenic causes (see Chap. 18, Fallopian Tube Anomalies). Additionally, a small subset of tubal infertility is idiopathic. Not only the cause of tubal damage, but also the nature of an anatomic abnormality is important. For example, proximal tubal occlusion, distal tubal occlusion, and tubal absence differ markedly in their treatment.

Proximal tubal occlusion describes obstruction proximal to the fimbria and may develop at the tubal ostium, isthmus, or ampulla. Specifically, *midtubal occlusion* is considered a subset of proximal occlusion. Proximal tubal occlusion may be secondary to tubal resection, luminal obliteration, or simply plugging with mucus or debris. In contrast, *distal tubal occlusion* describes obstruction at the tube's fimbria. It typically results from prior pelvic infection and may be associated with concomitant adnexal adhesions.

Tubal Cannulation

Proximal tubal occlusion is often amenable to direct techniques. If diagnosed at the time of hysterosalpingography (HSG), consideration should be given to performing concurrent selective salpingography (see Chap. 2, Selective Salpingography). A catheter is placed such that it wedges within the tubal ostium. This allows significantly greater hydrostatic pressure to be applied to the tube. Such pressure will likely overcome most instances of tubal spasm or plugging by mucus or debris. If patency of the tube cannot be established, an inner catheter with guidewire is used to cannulate the tube. This creates patency of isolated short segmental scarring in most instances. Scarring of a longer segment or luminal obliteration, however, is not amenable to correction with tubal cannulation. In these women, surgical segmental resection and reanastomosis or IVF may be considered.

TUBAL RECONSTRUCTION

Proximal Tubal Obstruction

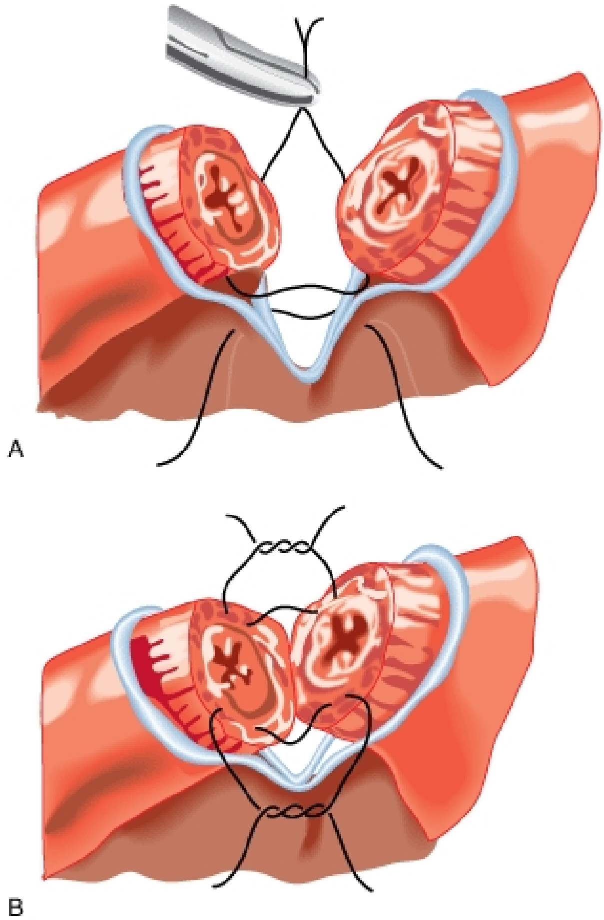
Tubal obstruction not amenable to treatment with selective salpingography has traditionally been treated surgically, and options include hysteroscopic cannulation, surgical reanastomosis, and neosalpingostomy. Although there have been considerable increases in the success rates of ART, reproductive surgery remains an important option or complement to ART for many couples.

Some types of tubal blockage have a much better prognosis with surgical therapy than others. For example, hysteroscopic cannulation of fallopian tubes can treat some types of proximal obstruction in a fashion similar to selective salpingography (see Section 41-40, Hysteroscopic Proximal Fallopian Tube Cannulation). Hysteroscopic cannulation is best performed with concurrent laparoscopy to verify distal tubal patency.

Proximal obstruction not amenable to cannulation techniques can be treated with segmental resection and reanastomosis. In most cases, this can be done as an outpatient procedure through a mini-laparotomy incision. However, obstruction extending into the interstitial portion of the tube is more technically challenging to repair and more prone to obstruction postoperatively. Therefore, proximal occlusion extending to the interstitial segment that cannot be treated with cannulation is best treated in most instances with IVF.

Proximal and midtubal occlusion resulting from prior sterilization can be treated with either tubal reanastomosis or IVF (Fig. 20-7). From a patient perspective, outpatient tubal reanastomosis avoids ovarian stimulation and increased risk for multifetal gestation and provides an ability to conceive normally. In general, although the monthly probability of pregnancy following tubal reversal is likely lower than age-matched controls without prior sterilization, the cumulative chance of pregnancy is high. However, IVF should be strongly considered if other fertility factors are present or the type of sterilization performed does not permit reconstruction. For example, in cases of sterilization completed by fimbriectomy, neosalpingostomy can be corrective, however, the probability of pregnancy is lower and IVF should be considered.

FIGURE 20-7



Surgical reanastomosis of fallopian tube segments. The scarred portion of the tube is sharply excised until nonfibrotic tubal tissues are reached. **A.** The mesosalpinx is re-approximated with interrupted stitches using 6-0 delayed-absorbable suture. **B.** The tubal muscularis is re-approximated with single stitches in each quadrant using 7-0 delayed-absorbable suture. Tubal serosa is closed with interrupted or running 6-0 delayed-absorbable suture.

The reversibility of sterilization can generally be determined by review of the operative report and pathology report if the procedure involved segmental resection. If operative records are unavailable or suggest that reanastomosis may not be feasible, laparoscopy is performed prior to laparotomy to assess chances of surgical success.

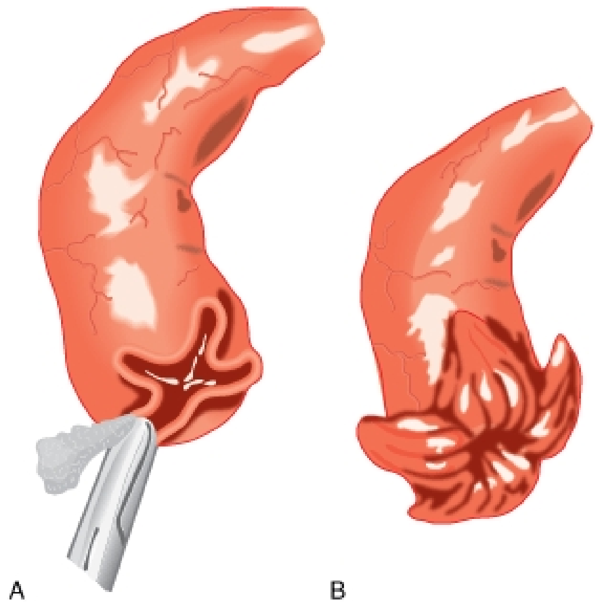
Outpatient reversal of sterilization is most commonly done by mini-laparotomy. Incision size typically varies from 3 to 6 cm, depending on a patient's weight and anatomy. Some surgeons are able to complete some of these procedures by laparoscopy. Robotic control may be helpful for this, but may increase operating time and expense.

Distal Tubal Obstruction

Following pelvic inflammatory disorders, normal fimbrial anatomy may be destroyed or fimbria may be encased by concomitant adnexal adhesions. In these cases, neosalpingostomy can be performed at mini-laparotomy or laparoscopy (Fig. 20-8). However, women desiring neosalpingostomy for treatment of distal occlusion should be counseled that the risk of ectopic pregnancy is high, the likelihood of pregnancy is 50 percent or lower, and postoperative re-occlusion is common (Bayrak, 2006). Moreover, hydrosalpinges that are dilated more than 3 cm in diameter, that are associated with significant adnexal adhesions, or that display an obviously attenuated endosalpinx yield a poor prognosis. These tubes are best treated by salpingectomy and plans for IVF. If both tubes are affected, bilateral salpingectomy is recommended prior to proceeding with IVF to improve IVF pregnancy rates

(Practice Committee of the American Society of Reproductive Medicine, 2004b).

FIGURE 20-8



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Neosalpingostomy. **A.** The distal end of the clubbed fallopian tube is opened sharply or with electric or laser energy. **B.** The endosalpinx is everted using Cuff or Bruhat technique.

CORRECTION OF UTERINE FACTORS

Three types of uterine factors have been implicated in infertility and include leiomyomas, endometrial polyps, and intrauterine adhesions. Mechanisms of infertility with these factors have not been clearly elucidated, however, the end result is decreased endometrial receptivity and reduced likelihood of embryo implantation.

Leiomyomas

Leiomyomas are common benign tumors of the uterus and have been associated with infertility in some women. Retrospective studies have suggested a benefit from surgically removing these tumors to increase efficacy of both natural and assisted conception (Griffiths, 2006).

There are no randomized controlled trials to clearly demonstrate that myomectomy improves fertility. However, in view of the many retrospective observational studies that suggest this, it is reasonable to offer myomectomy to infertile women, especially if tumors are large or impinge on the endometrial cavity. Myomectomy can be performed using hysteroscopy, laparoscopy, or via laparotomy, and selection of the approach is discussed in Chapter 9, Surgical Management. Currently, no studies validate one method compared with another in terms of efficacy. Therefore, clinical judgment should determine the most appropriate technique from the standpoint of safety, restoration of normal uterine anatomy, and speed of recovery.

Endometrial Polyps

These soft fleshy endometrial growths are commonly diagnosed during evaluation of infertility. Several studies have suggested good pregnancy rates following polypectomy, although the mechanism by which polyps may impair fertility has not been established. The requirement to remove even small polyps in infertile women has been previously debated. However, a recent prospective trial of 204 women with polyps and with an additionally diagnosed cervical factor, male factor, or unexplained infertility

appears to give some clear guidance with regard to this issue.

In this trial, women were randomized to one of two groups prior to treatment with intrauterine insemination (IUI) (PÃ©rez-Medina, 2005). The first group underwent polypectomy. The second underwent only hysteroscopic biopsy of the polyp to obtain histologic confirmation. All patients were managed expectantly for three cycles prior to proceeding with up to four cycles of IUI. The pregnancy rate in the polypectomy group was more than twice as high regardless of polyp size (Table 20-6). These data suggest that endometrial polyps can significantly impair outcome of infertility treatment. Thus, it would seem prudent to perform hysteroscopic polypectomy in all infertile women if a polyp is identified (Section 41-38, Polypectomy).

Table 20-6 Number and Percentage of Pregnancies after Hysteroscopic Polypectomy (*n* = 204)

	Polypectomy *n = 101 (%)*	**Control *n = 103 (%)***	***p-value***
Subsequent pregnancy	64 (63.4)	29 (28.2)	<0.001

RR 2.1 (95% CI 1.5â€“2.9).

From Perez-Medina, 2005, with permission.

Intrauterine Adhesions

Adhesions within the endometrial cavity, also called *synechiae,* can range from asymptomatic small bands to complete or near complete obliteration of the endometrial cavity. If amenorrhea or hypomenorrhea result, the condition is termed *Asherman syndrome* (see Chap. 18, Asherman Syndrome).

Treatment involves surgical adhesiolysis to restore normal uterine cavity size and configuration. Dilatation and curettage (D&C) and abdominal approaches have previously been used. However, with the advantages of hysteroscopy, the role of these techniques has been minimized (see Section 41-41, Lysis of Intrauterine Adhesions).

Hysteroscopic adhesion resection may range from simple lysis of a small band to extensive adhesiolysis of dense intrauterine adhesions using scissors, electrosurgical cutting, or laser energy. However, women in whom the uterine fundus is completely obscured and those with a markedly narrowed, fibrotic cavity present the greatest therapeutic challenge. Several techniques have been described for these difficult cases, but outcome is far worse than in patients with small band adhesions. In women with severe Asherman syndrome that is not amenable to reconstructive surgery, gestational carrier surrogacy is a valuable option.

TREATMENT OF PERITONEAL DISEASE

Endometriosis and pelvic adhesions are two types of peritoneal disease that frequently contribute to infertility and that may develop independently or concurrently.

Endometriosis

This condition and its effects on infertility are extensively discussed in Chapter 10, Infertility. In women with minimal or mild disease, evidence supporting lesion ablation is limited, and use of empiric general fertility boosting procedures such as ART or superovulation combined with IUI is reasonable. These treatments have been validated to increase fecundity in women with stage I and II disease (Table 20-7) (Guzick, 1999).

Table 20-7 Cycle Fecundity in Women with Stage I or II Endometriosis, According to Treatment					
Group	**Unexplained Infertility**	**Endomentriosis-associated Infertility**			
Treatment	**Guzick**[a]	**Deaton**[a]	**Chaffin**[a]	**Fedele**[a]	**Kemmann**[a]
No treatment or intracervical insemination	0.02	0.033	â€”	0.045	0.028
IUI	0.05[b]	â€”	â€”	â€”	â€”
Clomiphene	â€”	â€”	â€”	â€”	0.066
Clomiphene/IUI	â€”	0.095[b]	â€”	â€”	â€”
Gonadotropins	0.04[b]	â€”	0.066	â€”	0.073[b]
Gonadotropins/IUI	0.09[b]	â€”	0.129[b]	0.15[b]	â€”
IVF	â€”	â€”	â€”	â€”	0.222[b]

[a] And their colleagues.

[b] $p < .05$ for treatment vs. no treatment.

IUI = intrauterine insemination; IVF = in vitro fertilization.

From American Society of Reproductive Medicine, 2004a, with permission.

Moderate and severe endometriosis results in distortion of anatomic relationships of reproductive organs. In many cases, surgical treatment may improve anatomy and pregnancy may result (Practice Committee of the American Society of Reproductive Medicine, 2004a). Unfortunately, advanced disease may prevent adequate restoration of pelvic anatomy. Therefore, a surgeon's operative findings and anticipated surgical results should guide postoperative strategy. If a satisfactory surgical outcome is achieved, it is reasonable to attempt pregnancy for 6 to 12 months prior to considering other options such as IVF. It should be remembered that endometriosis in some cases may recur quickly, and unnecessary delay in attempting pregnancy postoperatively is not advised.

Several studies suggest that in women with advanced endometriosis, long-term treatment with a GnRH analog before initiation of a cycle may improve fecundity (Dicker, 1992; Surrey, 2002). At the present time, however, this treatment strategy is not universally accepted.

If endometriomas are noted, a surgeon may select: cyst drainage, drainage followed by cyst wall ablation, or cyst excision. All three procedures can be performed laparoscopically in nearly all circumstances given adequate surgeon experience. Simple drainage minimizes ovarian destruction, but most commonly results in rapid cyst recurrence. A recent study demonstrated that a mean of 60 percent of the cyst wall (range of 10 to 98 percent) was lined by endometrium to a depth of 0.6 mm (Muzii, 2007). Therefore, drainage and ablation is also associated with significant risk of cyst recurrence as well as thermal damage to the ovary. For these reasons, laparoscopic excision of the cyst wall by a stripping technique should be considered optimal treatment for most endometriomas (see Section 41-33, Laparoscopic Ovarian Cystectomy). However, excision is inevitably accompanied by removal of normal ovarian tissue in more than 80 percent of cases and often leads to decreased ovarian volume and diminished ovarian reserve.

Adhesions

Pelvic adhesions may result from endometriosis, prior surgery, or pelvic infection and often vary in their density and vascularity. Adhesions may impair fertility by distorting adnexal anatomy and interfering with gamete and embryo transport even in the absence of tubal disease.

Surgical lysis may restore pelvic anatomy in some cases, but adhesions may recur, especially if dense and vascular. Adherence to

microsurgical principles and minimally invasive surgery may help decrease adhesion formation. Although numerous adjuvants have been used to reduce the risk of postoperative adhesion formation, currently none have been validated to improve fecundity (Practice Committee of the American Society of Reproductive Medicine, 2006).

Among infertile women with adnexal adhesions, pregnancy rates after adhesiolysis are 32 percent and 45 percent at 12 and 24 months of surveillance, respectively, compared with 11 percent (at 12 months) and 16 percent (at 24 months) in those left untreated (Tulandi, 1990). As with severe endometriosis, clinical judgement regarding operative findings and results of surgery should guide the strategy postoperatively. In vitro fertilization is the best option for those with a poor prognosis for restoration of normal anatomy.

Correction of Cervical Abnormalities

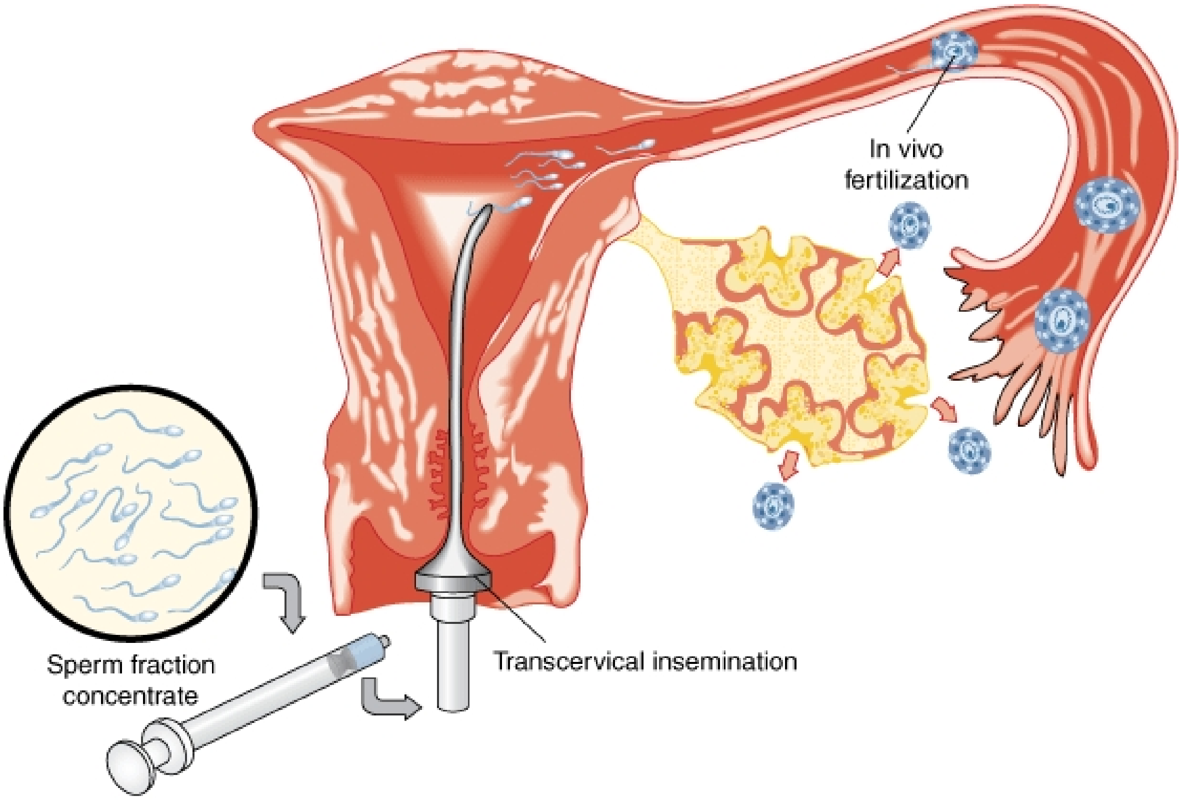
In response to follicular estradiol production, the cervix should produce abundant thin mucus. If present, this mucus acts as a conduit and functional reservoir for sperm (see Fig. 19-9). Accordingly, inadequate cervical mucus impairs sperm transport to the upper female reproductive tract.

Causes of abnormal or deficient mucus include infection, prior cervical surgery, use of anti-estrogens (e.g., clomiphene citrate) for ovulation induction, and sperm antibodies. However, many women with decreased or hostile mucus have no history of predisposing factors.

Examination of cervical mucus may reveal gross evidence of chronic cervicitis that deserves treatment. Alternatively, in those with decreased mucus volume, treatments include short-term supplementation with exogenous estrogen such as ethinyl estradiol and the use of the mucolytic expectorant, guaifenesin. However, the value of estrogen and guaifenesin has not been confirmed. Moreover, exogenous estrogens could have a negative effect on follicular development and ovarian function.

For these reason, most clinicians treat noninfectious, suspected cervical mucus abnormalities with IUI. Although this treatment also has not been validated in randomized prospective trials (Helmerhorst, 2005), the theoretical basis for this approach seems sound. Additionally, IUI has been demonstrated to be effective for treatment of unexplained infertility. As a result, many clinicians forgo cervical mucus testing and proceed directly with IUI treatments in the absence of tubal disease (Fig. 20-9).

FIGURE 20-9



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

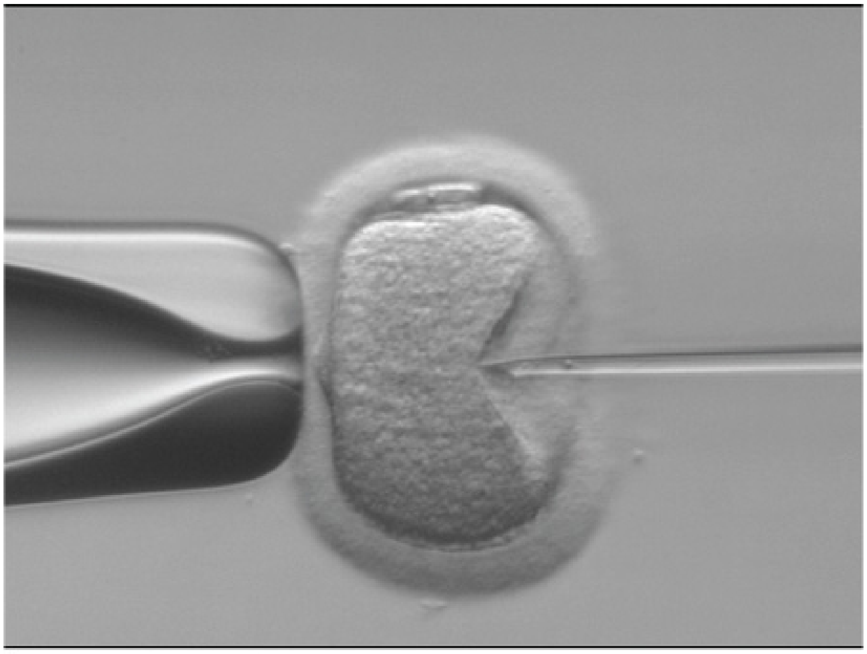
Intrauterine insemination (IUI). Prior to IUI, partner or donor sperm is washed and concentrated. Signs of impending ovulation are monitored with transvaginal sonography. At the time of suspected ovulation, a long, thin catheter is threaded through the cervical os and into the endometrial cavity. A syringe containing the sperm concentrate is attached to the catheter's distal end, and the sperm sample is injected into the endometrial cavity.

Correction of Male Infertility

Male infertility has varied causes and may include abnormalities of semen volume such as aspermia and hypospermia or of sperm number such as azoospermia and oligospermia. Additionally, motility may be limited, termed asthenospermia, or sperm structure may be abnormal, teratozoospermia. Accordingly, therapy should be planned only after thorough evaluation (see Chap. 19, Normal Spermatogenesis).

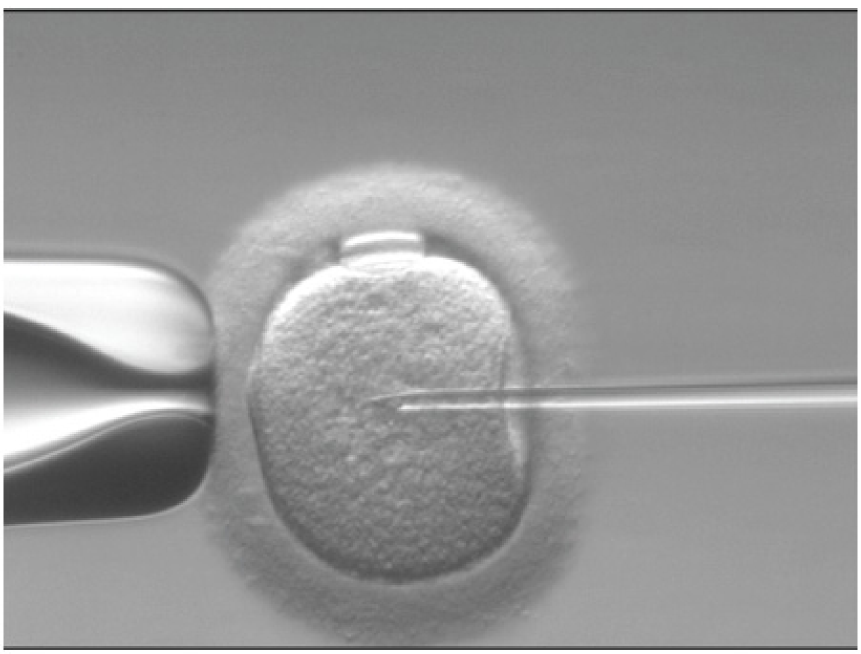
In the absence of an identifiable correctable cause for semen or sperm abnormalities, it is appropriate to offer IUI or ART as treatment options. The choice of whether to proceed initially with IUI as opposed to the more intensive and expensive ART treatments is dependent on several factors. These include duration of infertility, age of the female, and history of prior treatments. If ART is considered for male factors, intracytoplasmic sperm injection (ICSI) (Fig. 20-10) is typically selected rather than traditional IVF.

FIGURE 20-10



A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

A. and **B.** Photomicrographs of intracytoplasmic sperm injection.

ASPERMIA

This condition is characterized by a complete lack of semen and results from failure to ejaculate. The physiology of ejaculation includes emission of sperm with accessory gland fluid into the urethra, simultaneous closure of the urethral sphincters, and forceful ejaculation of semen through the urethra. Emission and closure of the bladder neck are primarily α-adrenergically mediated thoracolumbar sympathetic reflex events with supraspinal modulation. Ejaculation is a sacralspinal reflex mediated by the pudendal nerve.

Anejaculation or anorgasmia is not a rare complaint and may be related to psychogenic factors, organic erectile dysfunction, or impaired parasympathetic sacralspinal reflex. Appropriate treatments depend on the cause and may include psychological counseling or erectile dysfunction treatment with sildenafil citrate (Viagra, Pfizer, New York, NY) or other similar medication. Vibratory stimulation may also be effective in some instances. Electroejaculation is an invasive procedure and is generally used for men with spinal cord injuries that are unresponsive to the therapies above.

Men who achieve orgasm but never experience prograde ejaculation or have a greatly reduced prograde volume typically have retrograde ejaculation. Therefore, administration of oral pseudoephedrine or other α-adrenergic agent to aid bladder neck closure is warranted. However, for many, pharmacologic methods are ineffective, and IUI may be performed using sperm processed from a voided postejaculatory urine specimen.

A minority of men who achieve orgasm, but not prograde ejaculation, have failure of emission. Treatment with sympathomimetic agents may be attempted in these individuals as well, although pharmacologic therapies have generally met with limited success. Alternatively, testicular or epididymal extraction of sperm via aspiration or biopsy may be used in cases refractory to medication. As with electroejaculation, this technique recovers a limited number of viable sperm and is best suited for use with ICSI.

HYPOSPERMIA

Hypospermia or low semen volume (less than 2 mL) impairs transport of sperm into cervical mucus and may be associated with decreased sperm density or motility. Retrograde ejaculation may underlie this condition and treatment follows that described for aspermia.

Alternatively, hypospermia may follow partial or complete ejaculatory duct obstruction. In these cases, transurethral resection of ejaculatory ducts has resulted in marked improvement in semen parameters, and pregnancies have been achieved. However, couples should be counseled that postoperative complete obstruction of the ejaculatory ducts is not rare. Thus, consideration should be given to cryopreservation of sperm prior to surgical attempts in those individuals with partial obstruction.

AZOOSPERMIA

Characterized by the total absence of sperm in semen, azoospermia may result from obstruction in the male reproductive tract or from nonobstructive causes.

Obstructive azoospermia, especially resulting from prior vasectomy or ejaculatory duct obstruction, may be amenable to surgical treatment. However, congenital bilateral absence of the vas deferens (CBAVD) is a common cause of azoospermia, and is unfortunately not treatable surgically. In such candidates, testicular sperm extraction (TESE) may be performed in conjunction with ICSI.

Nonobstructive azoospermia may be caused by a karyotypic abnormality such as Klinefelter syndrome (47,XXY) or balanced translocation, deletion of a small portion of the Y chromosome, testicular failure, or by unexplained causes. In many cases, TESE may be combined effectively with ICSI in those with Klinefelter syndrome and Y microdeletion of the AZFc region. However, in men with Y microdeletion in the AZFa or AZFb region, this ART combination has been ineffective (Choi, 2004).

OLIGOSPERMIA

Oligospermia is diagnosed if fewer than 20 million sperm are present per milliliter of semen. Causes are varied and include hormonal, genetic, environmental (including medications), and unexplained causes. Additionally, an obstructive cause, especially ejaculatory duct obstruction, should be considered if oligospermia is seen in conjunction with low semen volume. If severe oligospermia (<5 to 10 million sperm per mL) is noted, then an evaluation similar to that for azoospermia is warranted.

Oligospermia in the absence of decreased sperm motility not uncommonly reflects hypogonadotropic hypogonadism. In general, hypogonadotropic hypogonadism is best treated with injections of FSH and hCG. Alternatively, clomiphene citrate and aromatase inhibitors, although not FDA-approved treatment for this indication, may be considered in some instances, especially if obesity and elevated serum estradiol levels are present. Spermatogenesis is a long process lasting approximately 100 days, and several months may be required to identify significant improvements in sperm density with either treatment.

Environmental factors such as excessive exposure to high temperatures should be investigated. Drug and medication history should also be obtained. If an environmental factor is identified, correction may improve sperm numbers.

ASTHENOSPERMIA

Asthenospermia or decreased sperm motility may be seen alone or in combination with oligospermia or other abnormal semen parameters. In general, asthenospermia does not respond to directed treatments. Expectant management may be considered, especially if the duration of infertility is short, and maternal age is less than 35 years. For treatment, IUI and ICSI are preferred, although IUI is generally not successful in severe cases (Centola, 1997). If fewer than one million motile sperm are available for insemination following semen processing, or the couple has experienced more than 5 years of infertility, then ICSI should be considered as initial therapy (Ludwig, 2005a).

TERATOZOOSPERMIA

Teratozoospermia, that is, abnormal sperm morphology is most often seen in conjunction with oligospermia, asthenospermia, and oligoasthenospermia. Directed treatments for teratozoospermia are not available and therapy options include IUI and ART. Because teratozoospermia may commonly be accompanied by sperm function defects that may impair fertilization, ICSI should be considered if ART is selected.

VARICOCELE

This dilation of the blood vessels in the scrotum is usually left-sided and results from dilatation of the pampiniform plexus of the spermatic vein (see Fig. 19-3). Traditional treatment is surgical ligation of the internal spermatic vein. With ligation, several surgical techniques have been employed, but retroperitoneal high ligation or transinguinal ligation is the most frequently performed. More recently, interventional radiographic techniques that selectively catheterize and embolize the internal spermatic vein with sclerosing solutions, tissue adhesives, or detachable balloons or coils have been used as alternatives. Despite the widespread application of varicocele treatments, there is insufficient evidence to conclude that treatment of a clinical varicocele in couples with male subfertility improves the likelihood of conception (see Chap. 19, The Male History) (Evers, 2003).

UNEXPLAINED INFERTILITY

Unexplained infertility may represent one of the most common infertility diagnoses, with a reported prevalence of up to 30 percent (Dodson, 1987). The diagnosis of unexplained infertility is highly subjective and depends on the diagnostic tests performed or omitted and on their level of quality. Paradoxically, a diagnosis of unexplained infertility, therefore, will be more often reached if the evaluation is incomplete or of poor quality (Gleicher, 2006). Nevertheless, a diagnosis of unexplained infertility can, by definition, not be directly treated. Expectant management may be considered, especially with infertility of short duration and with relatively young maternal age. However, if treatment is desired, then IUI, superovulation, and ART are empiric appropriate interventions to consider.

INTRAUTERINE INSEMINATION

This technique processes semen and separates motile, morphologically normal spermatozoa from dead sperm, leukocytes, and seminal plasma. This highly motile fraction is then inserted transcervically via a flexible catheter near the anticipated time of ovulation (Fig. 20-9). Intrauterine insemination can be performed with or without superovulation (SO) and is appropriate therapy for treatment of cervical factors, mild and moderate male factors, and unexplained infertility.

If performed for cervical factors, IUI timed by urine LH surge is an initial strategy that achieves reasonable pregnancy rates of up to 11 percent per cycle (Steures, 2004). Although this rate is lower than that seen with SO combined with IUI, SO side effects and costs are avoided.

In contrast, for unexplained infertility and for male factors, IUI is most commonly performed in conjunction with SO. A combination of clomiphene citrate and IUI was evaluated by Deaton and colleagues (1990) in a randomized trial. In this study, the treatment group had a significantly higher pregnancy rate (9.5 percent) compared with controls (3.3 percent). Gonadotropin treatment (FSH or hMG) alone has been shown to increase the likelihood of pregnancy, but the benefit is markedly improved with the addition of IUI.

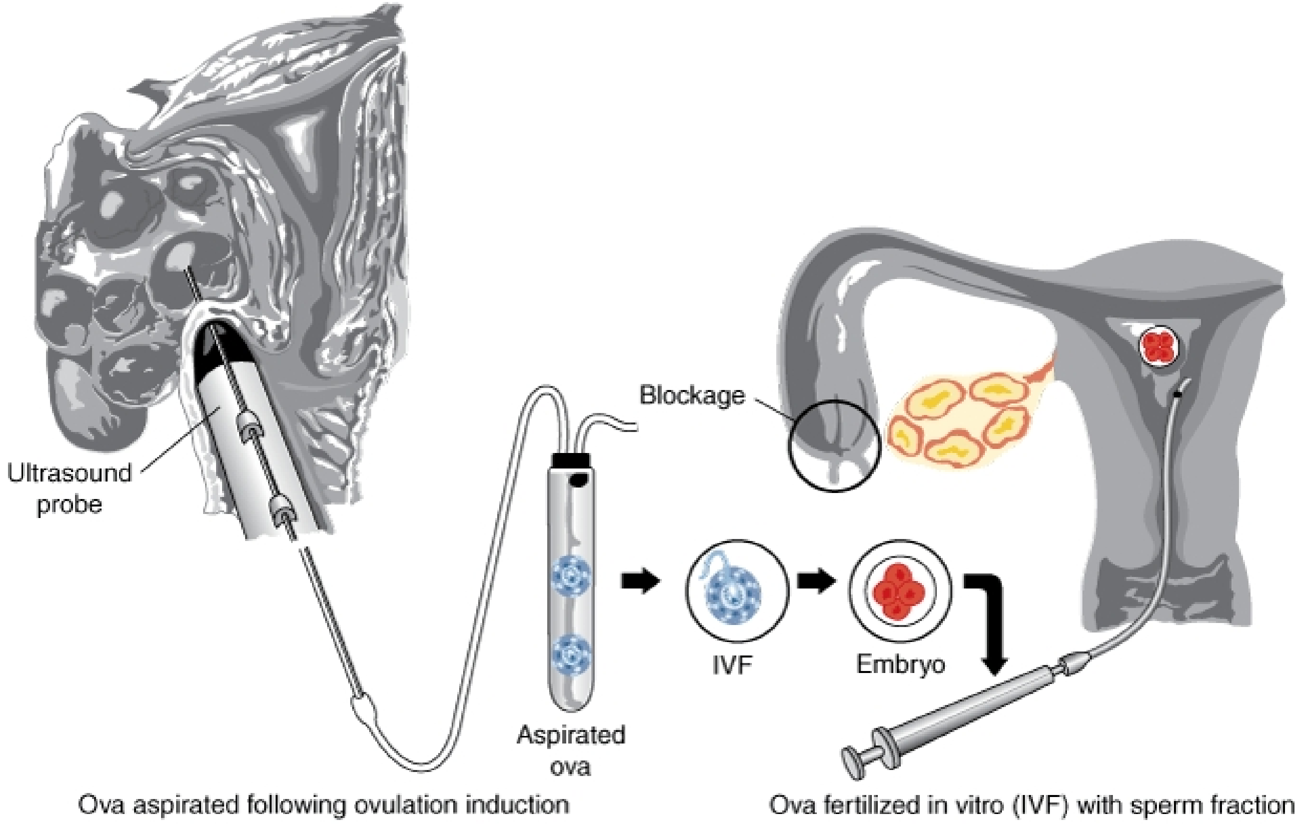
ASSISTED REPRODUCTIVE TECHNOLOGIES

Assisted reproductive technologies describes clinical and laboratory techniques used to achieve pregnancy in infertile couples for whom direct corrections of underlying causes are not feasible. In principle, IUI meets this definition. By convention, however, ART procedures are those that at some point require extraction and isolation of an oocyte. These techniques include, but are not limited to, in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), egg donation, gestational carrier surrogacy, gamete intrafallopian transfer (GIFT), and zygote intrafallopian transfer (ZIFT). Additional ART-associated techniques include egg and embryo cryopreservation, testicular sperm extraction (TESE), in vitro maturation of oocytes (IVM), and pre-implantation genetic diagnosis (PGD).

In Vitro Fertilization

During IVF, mature oocytes from stimulated ovaries are retrieved transvaginally with sonographic guidance (Figs. 20-11 and 20-12). Sperm and ova are then combined in vitro to prompt fertilization (Fig. 20-13). If successful, viable embryos are transferred transcervically into the endometrial cavity using sonographic guidance (Fig. 20-14).

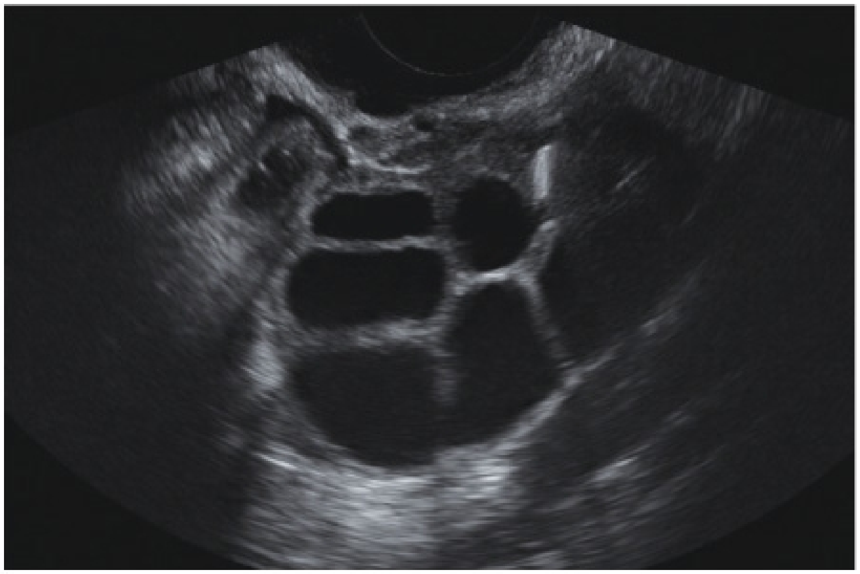
FIGURE 20-11



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

In vitro fertilization (IVF). Superovulation is induced with one of the protocols displayed in Figures 20-2 and 20-3, and follicle maturation is monitored over several days sonographically. Near ovulation, a transvaginal approach is used to harvest eggs from the ovaries. These oocytes are fertilized in vitro and fertilized eggs develop to the blastocyst stage. Blastocysts are then drawn up into a syringe and delivered into the endometrial cavity.

FIGURE 20-12



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

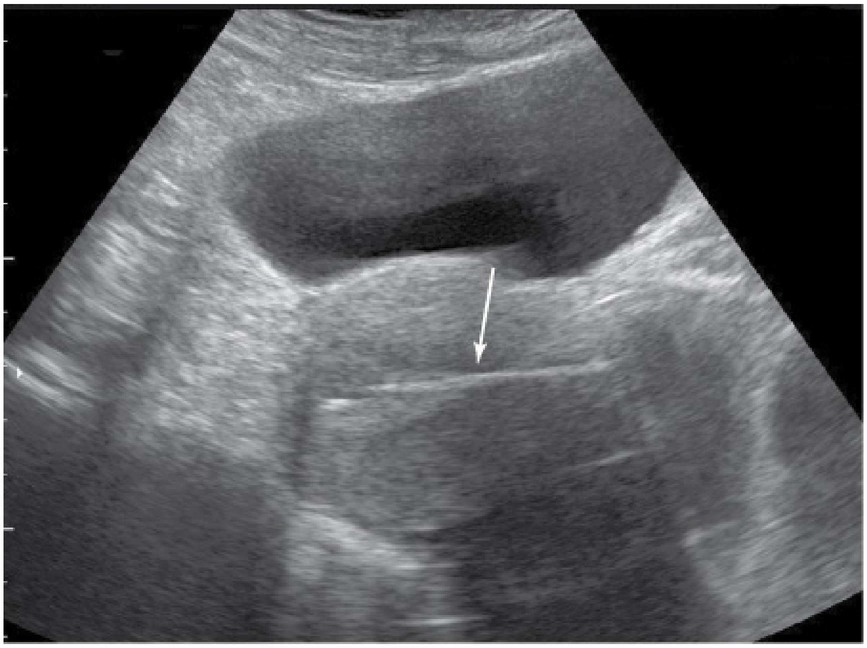
Transabdominal sonogram demonstrates transvaginal oocyte retrieval. The needle is seen in the upper right portion of the image as a hyperechoic line (**arrow**) entering a mature follicle.

FIGURE 20-13

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photograph displays the sterile laboratory environment required for in vitro fertilization: incubators, modified pediatric isolette, and micromanipulation station.

FIGURE 20-14



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Embryo transfer performed using abdominal sonographic guidance for proper placement. Catheter (arrow) is seen within the endometrial cavity.

Similarly to IUI, substantial benefit is achieved using controlled ovarian hyperstimulation (COH) prior to egg retrieval. Many ova are genetically or functionally abnormal, and thus exposure of several ova to sperm results in an increased chance of a healthy embryo.

Most often, GnRH analogs are used in conjunction with gonadotropins (FSH or hMG) to prevent the possibility of spontaneous LH surge and ovulation prior to egg retrieval. Optimally, 10 to 20 ova are harvested, and from these, ideally one healthy embryo is transferred.

Unfortunately, methods to determine embryo health are imperfect. Therefore, to maximize the probability of pregnancy, more than one embryo is typically transferred, thus resulting in increased risk of multifetal gestation. More recently, advances in culture conditions permit embryos to be cultured to the blastocyst stage, which allows transfer of fewer embryos, yet maintains high pregnancy rates (Langley, 2001).

As discussed in Chapter 9, Hydrosalpinx, hydrosalpinges should be removed or tubal interruption performed prior to proceeding with IVF to increase implantation rates and decrease the risk of miscarriage.

Intracytoplasmic Sperm Injection

This variation on IVF is most applicable to male factor infertility. During the micromanipulation technique of ICSI, cumulus cells surrounding the ova are enzymatically digested, and a single sperm is directly injected through the zona pellucida and oocyte cell membrane (Fig. 20-10). Pregnancy rates with ICSI are comparable with those achieved with IVF for other causes of infertility.

For azoospermic men, ICSI has made pregnancy possible. In these cases, sperm are mechanically extracted from the testicle or epididymis.

Gestational Carrier Surrogacy

This variation on IVF places a fertilized egg into the uterus of a surrogate, rather than into the intended mother. Indications are varied, and this approach may be appropriate for women with uncorrectable uterine factors, for those in whom pregnancy would pose significant health risks, and for those with repetitive unexplained miscarriage.

Gestational carrier surrogacy has legal and psychosocial issues. In most states, a surrogate is the legal parent, and therefore adoption must be completed after birth to give the intended mother her parental rights. However, a few states have adopted specific laws that extend protection to the intended parents.

Egg Donation

Egg donation may be employed in cases of infertility associated with ovarian failure or diminished ovarian reserve. Additionally, this technique may also be used to achieve pregnancy in fertile women when offspring would be at risk for maternally transmitted genetic disease. Egg donors may be known to the recipient couple, or more commonly are anonymous young women recruited by an agency or IVF center.

At present, the highest success rates require the use of "fresh" or noncryopreserved oocytes. For this reason, an egg donation cycle requires synchronization of a recipient's endometrium with egg development of the donor. Commonly, if a recipient is not menopausal, GnRH agonists are used to suppress gonadotropin production and allow for a controlled artificial cycle. Following suppression, exogenous estrogen is given beginning just prior to the start of gonadotropin administration to an egg donor. After a donor receives hCG to allow the final stages of follicle and egg maturation, the recipient begins progesterone. In the recipient, estrogen and progesterone are typically continued until late in the first trimester when placental production of these hormones is deemed to be adequate.

Gamete Intrafallopian Transfer

This technique is similar to IVF in that egg retrieval is performed after COH. Unlike IVF, however, fertilization and early embryo development does not take place in the laboratory. Eggs and sperm are placed via catheter through the fimbria and deposited directly into the oviduct. This transfer of gametes is most commonly performed at laparoscopy. Like IUI, GIFT is most applicable for unexplained infertility and should not be considered for tubal factor causes of infertility.

This technique was most popular in the late 1980s and early 1990s. However, as laboratory techniques have improved, IVF has largely replaced GIFT. In general, GIFT is more invasive, provides less diagnostic information, and requires transfer of more than two eggs for optimal pregnancy chances, which increases the risk of higher-order multifetal gestation. Thus, the major indication for GIFT at present is to avoid the religious or ethical concerns that some patients may have with fertilization taking place outside the body.

Zygote Intrafallopian Transfer

This technique is a variant of IVF with similarities to GIFT. Embryo transfer is not performed directly into the uterine cavity, but rather into the fallopian tube at laparoscopy. If the transfer is completed after an embryo has begun to divide, the procedure is more accurately termed *tubal embryo transfer* (TET). Although a normal fallopian tube may provide a superior environment for the early-stage embryo, this advantage has been lessened with improvements in laboratory culture methods. Accordingly, ZIFT currently should be considered most appropriately in the rare case in which transcervical transfer during IVF is technically not feasible.

Embryo Cryopreservation

With IVF, many eggs are retrieved to have ultimately one to three healthy embryos for transfer. This frequently leads to extra embryos. Successful freezing and thawing of embryos has been possible for two decades. Advances in cryoprotectants and techniques have allowed improved survival rates of embryos frozen at a variety of developmental stages. With cryopreservation, these supernumary embryos can yield pregnancies later, obviating the need for ovarian stimulation and egg retrieval.

Oocyte Cryopreservation

Significant technical challenges have been encountered with cryopreservation of unfertilized eggs. At this time, oocyte

cryopreservation is still considered by most to be experimental and long-term outcomes are unknown. This technique, however, is proving useful in attempting to preserve the fertility potential of women facing gonadotoxic chemotherapy (Marhhom, 2007). As success improves, oocyte cryopreservation may assist women desiring to delay childbearing and will likely lead to expansion of egg donation programs.

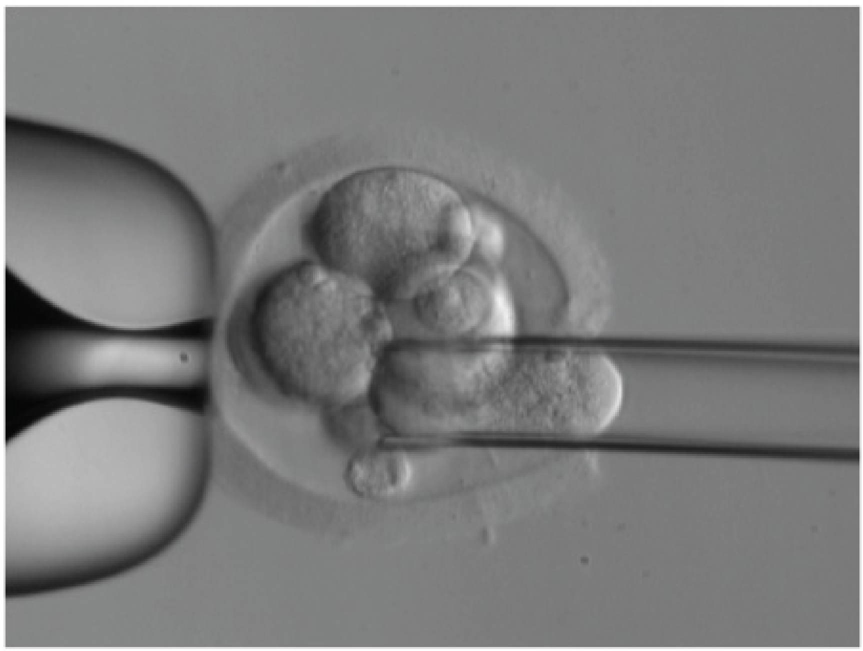
In Vitro Maturation

This technique has been used to achieve pregnancy by aspirating antral follicles from unstimulated ovaries and culturing these immature oocytes to allow resumption and completion of meiosis in vitro. Currently, IVM is considered experimental and long-term outcomes are unknown. This technique may be useful in patients with PCOS in whom stimulation poses a significant risk of OHSS. Additionally, it is possible that refinement and evolution of this technique may make possible maturation of ova from pre-antral follicles. This could potentially allow preservation of fertility potential for women in whom gonadotoxic chemotherapy is required.

Pre-Implantation Genetic Diagnosis

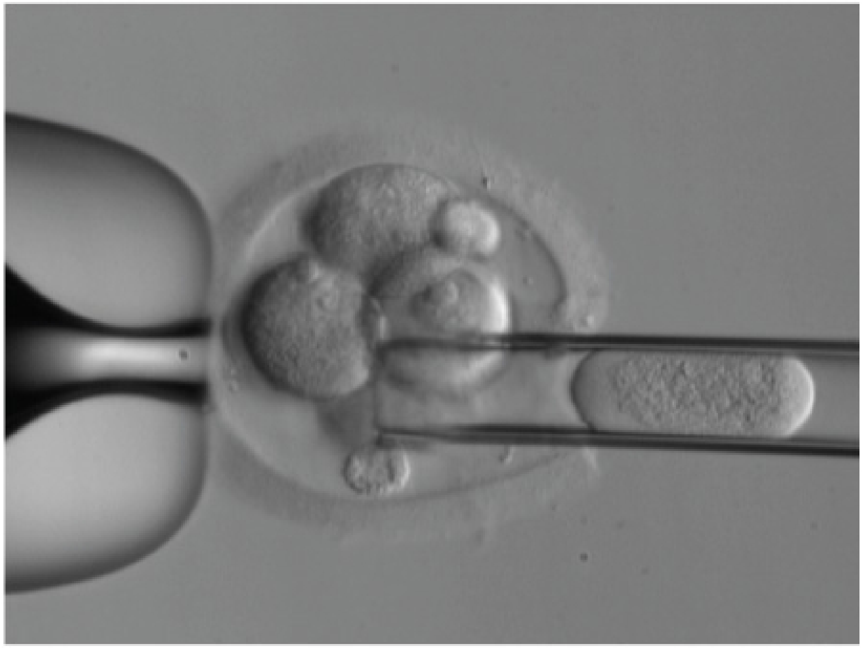
This laboratory technique removes cells from a developing embryo for screening of genetic disease. Typically performed by removing one or two cells at the six- to eight-cell stage, this technique can screen for single gene defects, unbalanced translocations, and aneuploidy (Fig. 20-15). Pre-implantation genetic diagnosis is considered an experimental procedure at this time, and implementation of newly developed methods for genetic analysis will likely continue to broaden its application.

FIGURE 20-15



A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



B

A. and **B.** Photomicrographs of embryo biopsy.

Complications of Assisted Reproductive Technologies

Assisted reproductive technologies in most cases lead to successful delivery of healthy singleton pregnancies. However, there are complications of pregnancy that may develop more frequently in those conceived using ART. Of these, risk of multifetal gestation is the most common. However, risks of prematurity or fetal growth restriction that is independent of maternal age and fetal number are also increased. In addition, increased rates of major congenital defects, epigenetic abnormalities, and placenta previa have been noted in IVF-conceived pregnancies (Ludwig, 2005b; Olson, 2005). Accordingly, in view of the above increased risks, it is reasonable to consider more intensive prenatal assessment in pregnancies conceived by IVF.

Fortunately, currently available data suggest that there are no differences between the psychomotor development of preschool children conceived by IVF and naturally conceived children. Similarly, the socio-emotional development of children conceived by IVF in this age group appears comparable with that of naturally conceived children (Ludwig, 2006).

CONCLUSION

The treatment of infertility should be initiated only after a thorough investigation as outlined in the Chapter 19. The initial focus should be to identify lifestyle or environmental issues that may contribute to or cause reproductive impairment. Obesity, adequate nutrition, and associated stress should not be overlooked. In general, it is desirable to correct any identifiable contributors to subfertility. In many cases, no obvious cause can be detected. In other couples, a cause may be identifiable, but not amenable to directed corrective therapies. In these circumstances, generalized fertility-boosting strategies may be recommended. These treatments include intrauterine insemination (with or without superovulation) and assisted reproductive technologies (ART).

It is important to recognize that superovulation and ART are not without risks and couples should be appropriately counseled. Additionally, these techniques may involve third parties (egg, sperm, or embryo donors or gestational carriers). These procedures are associated with unique psychosocial, legal, and ethical considerations. Emerging technologies such as preimplantation genetic testing bring additional ethical issues that must be confronted and resolved by both patient and practitioner.

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MENOPAUSAL TRANSITION: INTRODUCTION

The menopausal transition is a progressive endocrinologic continuum that takes reproductive-aged women from regular, cyclic, predictable menses that are characteristic of ovulatory cycles, to a final menstrual period associated with ovarian senescence and menopause. With improvements in medical treatment and increased focus on preventive health care, average life expectancy has increased. Most women can now expect to live at least one third of their lives in the menopause. Specifically, it is projected that by 2020, approximately 52 million women will be aged 55 years and older (U.S. Census Bureau, 2000). Thus, this age group has aptly been called "the next frontier in women's health care", as health and well-being is an important concern for this large and growing population of American women (Frackiewicz, 2000).

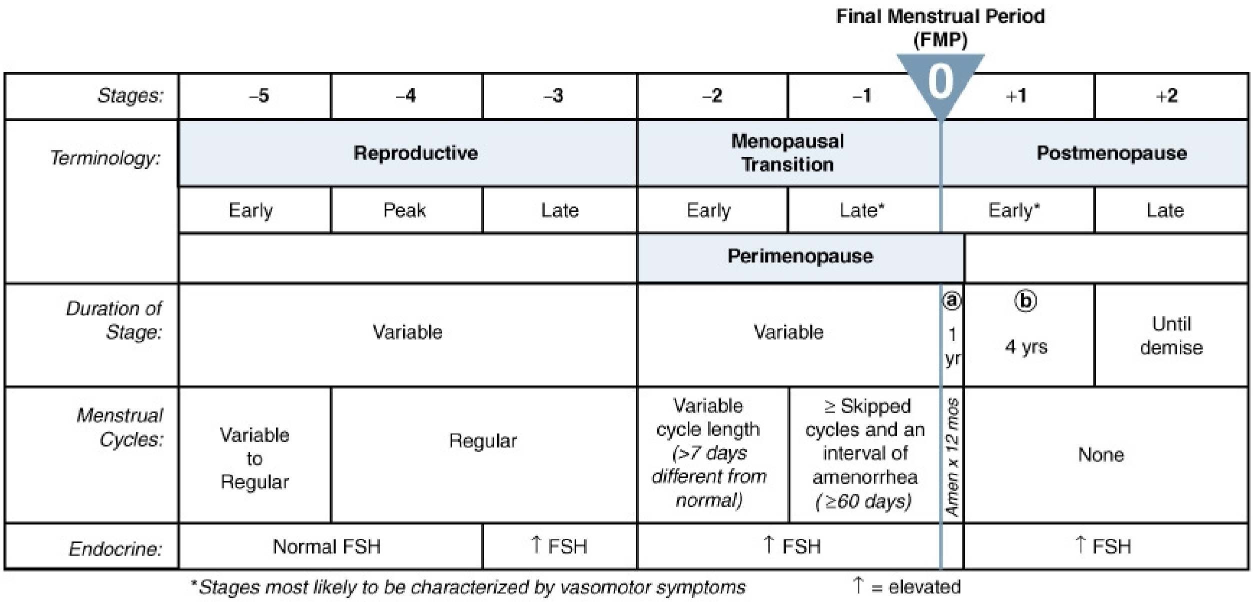
DEFINITIONS

The term *menopause* refers to a point in time that follows 1 year after the cessation of menstruation. The *postmenopause* describes those years following this point. The average age of women experiencing their final menstrual period (FMP) is 51.5 years, but cessation of menses due to ovarian failure may occur at any age. *Premature ovarian failure* refers to cessation of menses before age 40 and is associated with an elevated follicle-stimulating hormone (FSH) level (see Chap. 16, Hypergonadotropic Hypogonadism (Premature Ovarian Failure)).

The older terms *perimenopause* or *climacteric* generally refer to the time period in the late reproductive years, usually late 40s to early 50s. Characteristically, it begins with menstrual cycle irregularity and extends to 1 year after permanent cessation of menses. The more correct terminology for this time is *menopausal transition* . This transition typically develops over a span of 4 to 7 years, and the average age at its onset is 47 years (McKinlay, 1992).

Menopausal transition has been divided into an early and a late phase by Soules and others at the Stages of Reproductive Aging Workshop (STRAW) held in July, 2001 (Fig. 21-1). The purpose of the STRAW report was to clarify the stages and nomenclature of normal female reproductive aging. The group concluded that because the terms *perimenopause* and *climacteric* are not used consistently, they should be used only with patients and in the lay press and not in scientific papers, and the term *menopausal transition* is the preferred term (Soules, 2001).

FIGURE 21-1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

The stages of reproductive aging. *(Redrawn from Soules, 2001, with permission).*

The STRAW report divides reproductive and post-reproductive life into several stages. The anchor for the staging system is the FMP, and the age range and duration of each stage varies. Five stages precede and two stages follow the FMP. Stage â€“5 refers to the early reproductive period, stage â€“4 to the reproductive peak, and stage â€“3 to the late reproductive period. Stage â€“2 refers to the early menopausal transition (MT) and stage â€“1 to the late MT. Stage +1a refers to the first year after FMP, stage +1b refers to years two to five postmenopause, and stage +2 refers to the ensuing later postmenopausal years.

In the early menopausal transition (stage â€“2), a woman's menstrual cycles remain regular, but the interval between cycles may be altered by 7 or more days. Typically, cycle lengths become shorter. Compared with younger women, FSH levels are elevated, and serum estrogen levels may be increased in the early follicular phase. Normal ovulatory cycles may be interspersed with anovulatory cycles during this transition, and conception can occur unexpectedly. The late menopausal transition (stage â€“1) is characterized by two or more skipped menses and at least one intermenstrual interval of 60 days or more due to longer and longer periods of anovulation (Soules, 2001).

All of the above definitions are currently the best description of a woman's transit through menopause, but will certainly be subject to modification in the future.

INFLUENTIAL FACTORS

A number of environmental, genetic, and surgical influences may alter ovarian aging. For example, Wallace and associates (1979) found that smoking advances the age of menopause by about 2 years. In addition, chemotherapy, pelvic radiation, ovarian surgery may also lead to an earlier age of menopause. During the menopausal transition, more erratic fluctuations in female reproductive hormones can lead to an array of physical and psychological symptoms as outlined in Table 21-1 (Bachmann, 2001; Dennerstein, 1993).

Table 21-1 Symptoms Associated with Menopausal Transition

Changes in menstrual patterns

Shorter cycles are typical (by 2â€“7 days)
Longer cycles are possible
Irregular bleeding (heavier, lighter, with spotting)
Vasomotor symptoms
Hot flushes
Night sweats
Sleep disturbances
Psychological and metal disturbances
Worsening premenstrual syndrome
Depression
Irritability
Mood swings
Loss of concentration
Poor memory
Sexual dysfunction
Vaginal dryness
Decreased libido
Painful intercourse
Somatic symptoms
Headache
Dizziness
Palpitations
Breast pain and enlargement
Joint aches and back pain
Other symptoms
Urinary incontinence
Dry, itchy skin
Weight gain

PHYSIOLOGICAL CHANGES

Hypothalamus-Pituitary-Ovarian Axis Changes

During the reproductive life of a woman, gonadotropin-releasing hormone (GnRH) is released in a pulsatile fashion by the arcuate nucleus of the medial basal hypothalamus. It binds to GnRH receptors on the pituitary gonadotrophs to stimulate cyclic luteinizing hormone (LH) and FSH release. These gonadotropins, in turn, stimulate the production of the ovarian steroids: estrogen, progesterone, and also inhibin. During the reproductive years, estrogen and progesterone exert positive and negative feedback on pituitary gonadotropin production and on the amplitude and frequency of GnRH release. Produced in the granulosa cells, inhibin exerts important negative feedback influence over FSH secretion from the pituitary. This tightly regulated endocrine system leads to ovulatory menstrual cycles that are regular and predictable.

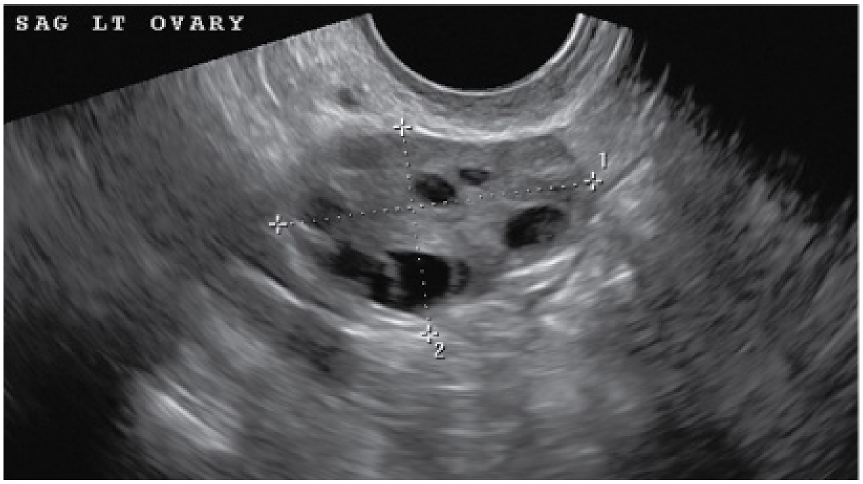
The transition from ovulatory cycles to menopause typically begins in the late 40s and in early menopausal transition (Stage â€“2). Levels of FSH rise slightly and lead to an increased ovarian follicular response with overall higher estrogen levels (Jain, 2005; Klein, 1996). There is an increase in serum estrogen levels, produced from an increased number of follicles in the stimulated cohort responding to rising FSH levels. Also, during this time ovarian follicles undergo an accelerated rate of loss until eventually, in the late menopausal transition, the supply of follicles is depleted. These changes, including the increase in FSH levels, reflect the reduced quality and capability of aging follicles to secrete inhibin (Santoro, 1996, Reyes, 1977). As follicular depletion continues, episodes of anovulation become more common (Roseff, 1989). With ovarian failure in the menopause (stage +1b), ovarian steroid hormone release ceases, and the negative-feedback loop is opened. Subsequently, GnRH is released at maximal frequency and amplitude. As a result, circulating FSH and LH levels rise up to fourfold higher than in the reproductive years (Klein, 1996).

Ovarian Changes

Ovarian senescence is a process that has been shown to actually begin in utero within the embryonic ovary due to programmed oocyte atresia (see Fig. 14-1). From birth onward, primordial follicles are continuously being activated, mature partially, and then regress. This follicular activation continues in a constant pattern that is independent of stimulation by the pituitary. Richardson and colleagues (1987) performed a quantitative histologic study of the endometrium and a randomly selected ovary. These were coupled with a single hormonal measurement and a reproductive history, from each of 17 women aged 44 to 55 years who underwent oophorectomy and hysterectomy for uterine leiomyomas or menorrhagia. The six women who reported regular cycles had an average of 1700 follicles in the selected ovary compared with an average of 180 follicles in the ovaries of those who reported irregular cycles. Evidence such as this suggests that regular follicular activation is altered during late reproductive life.

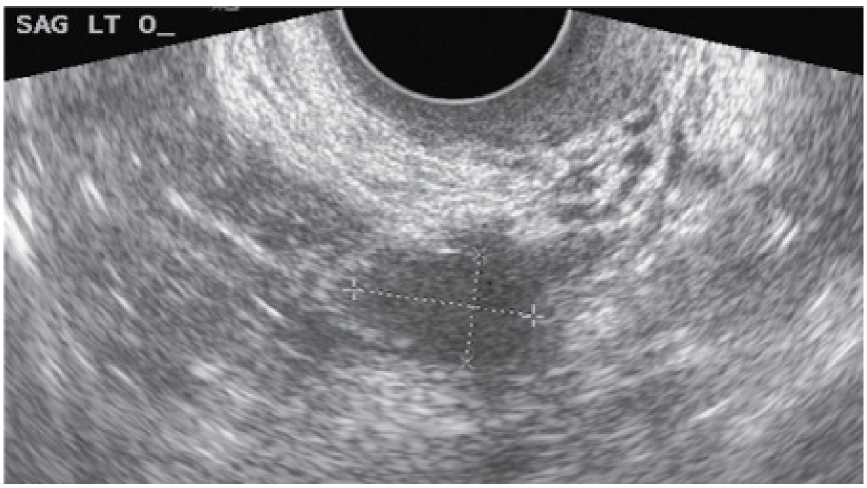
A more rapid depletion of ovarian follicles starts in the late 30s and early 40s and continues until a point at which the menopausal ovary is virtually devoid of follicles (Figs. 21-2 and 21-3). An average woman may experience about 400 ovulatory events during her reproductive lifetime. This represents a very small percentage of the 6 to 7 million oocytes present at the 20th week of gestation, or even the 700,000 oocytes present at birth. The process of atresia of the nondominant cohort of follicles, largely independent of menstrual cyclicity, is the prime event that leads to the eventual loss of ovarian activity and menopause.

FIGURE 21-2



A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

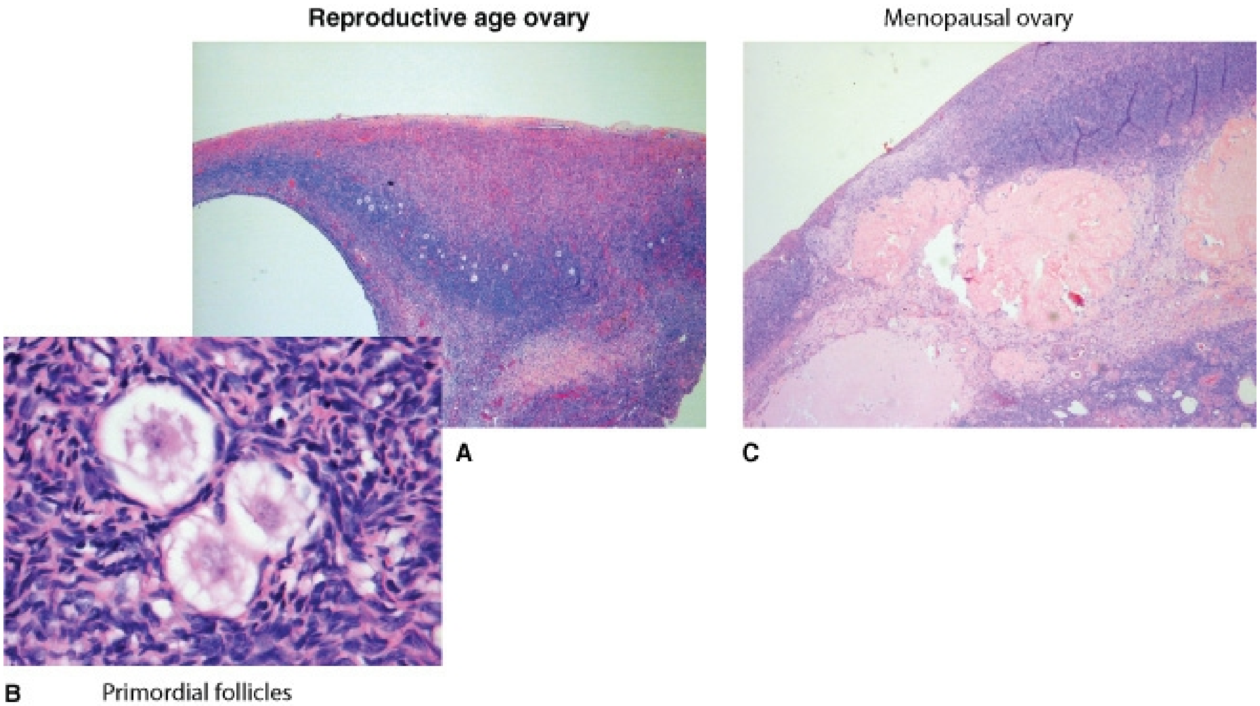


B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Transvaginal sonographic images of a pre- and postmenopausal ovary. **A.** In general, premenopausal ovaries have greater volume and contain follicles, which are seen as multiple, small, anechoic smooth-walled cysts. **B.** In comparison, postmenopausal ovaries have smaller volume and are characteristically devoid of follicular structures. *(Courtesy of Dr. Elysia Moschos).*

FIGURE 21-3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Microscopic differences between a reproductive-age and menopausal ovary. **A.** Reproductive-age ovary. Note preponderance of primordial follicles. **B.** High-power image of primordial follicles. **C.** The menopausal ovary shows abundance of atretic follicles and persistent corpora albicans. *(Courtesy of Dr. Raheela Ashfaq).*

Adrenal Steroid Level Changes

With advancing age, adrenal production of dehydroepiandrosterone sulfate (DHEAS) declines. Adrenal hormone levels have been studied in aging women by Labrie (1997) and Burger (2000), each with their colleagues. They found that in women aged 20 to 30 years, DHEAS concentrations peaked, with an average of 6.2 micromoles, and then decreased steadily. In women 70 to 80 years of age, DHEAS levels were diminished by 74 percent to 1.6 micromoles. Other adrenal hormones decrease with aging as well. Androstenedione peaks at ages 20 to 30 years and then decreases to 62 percent of this peak level in women aged 50 to 60 years. Pregnenolone diminishes by 45 percent from reproductive life to menopause. The ovary contributes to the production of these hormones during the reproductive years, but after menopause, only the adrenal gland continues this hormone synthesis.

Burger and associates (2000) prospectively studied 172 women during the menopausal transition as a part of the Melbourne Women's Midlife Health Project. By analyzing hormone levels longitudinally in these patients, no relationship between a woman's final menstrual period and the decline in DHEAS was noted. Advancing age, regardless of menopausal status, determined DHEAS decline.

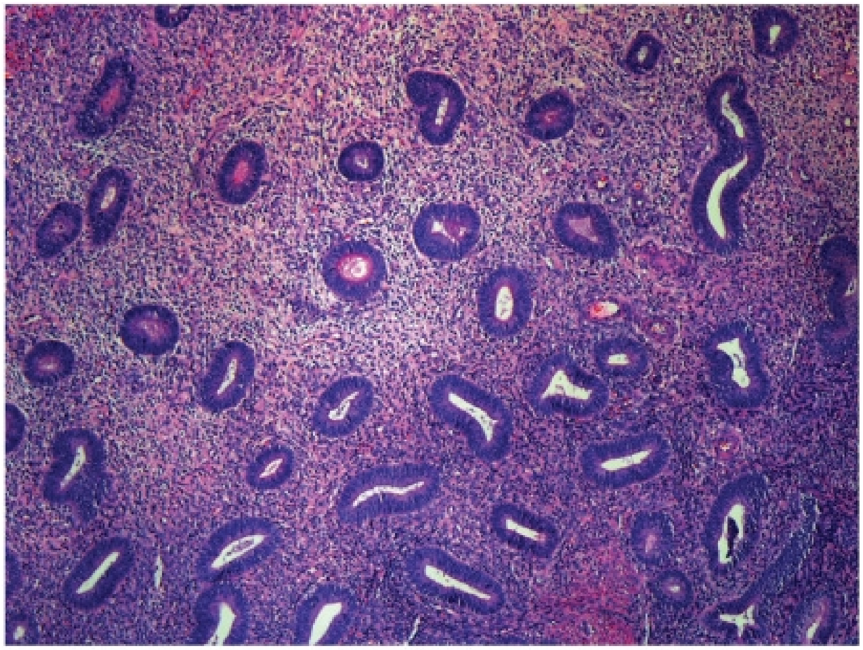
Sex Hormone-Binding Globulin Level Changes

The principal sex steroids, estradiol and testosterone, circulate in the blood bound to a glycoprotein carrier produced in the liver, known as sex hormone-binding globulin (SHBG). Production of SHBG declines after the menopause and may lead to increased levels of free or unbound estrogen and testosterone.

Endometrial Changes

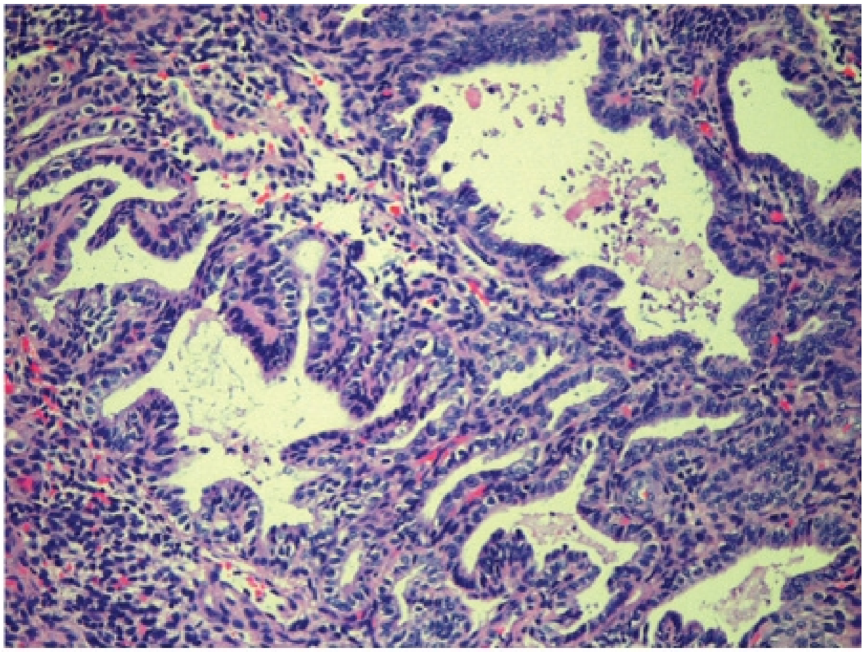
Microscopic changes in the endometrium directly reflect the level of systemic estrogen and progesterone and thus may change dramatically depending on the phase of menopausal transition. During early menopausal transition, the endometrium may reflect ovulatory cycles, which are prevalent during this time. During the later stage of menopausal transition, anovulation is common, and the endometrium will display estrogen's effect when unopposed by progesterone. Accordingly, proliferative changes or disordered proliferative changes are frequently findings on pathologic examination of endometrial biopsy samples. After menopause, the endometrium becomes atrophic due to lack of estrogen stimulation (Fig. 21-4).

FIGURE 21-4



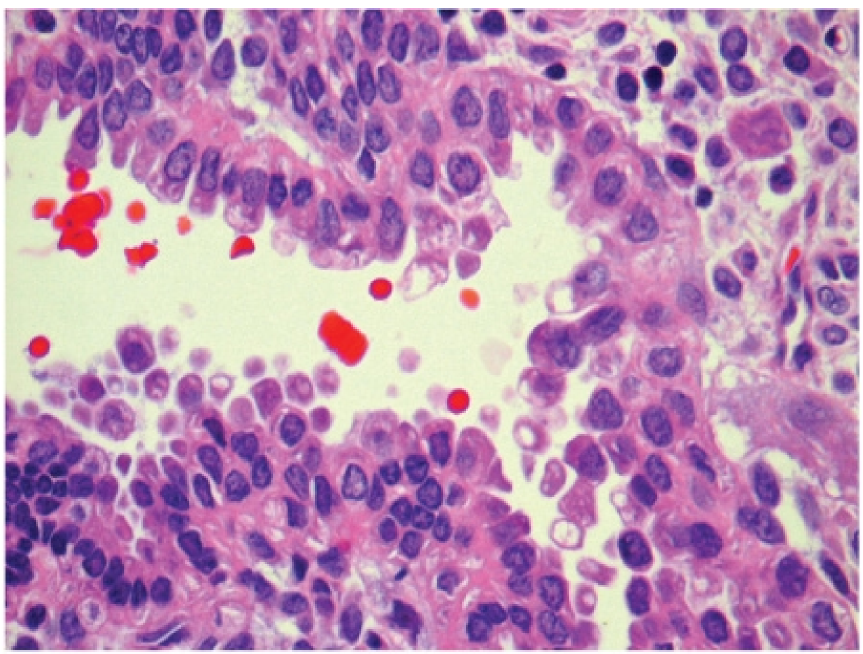
A Proliferative

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



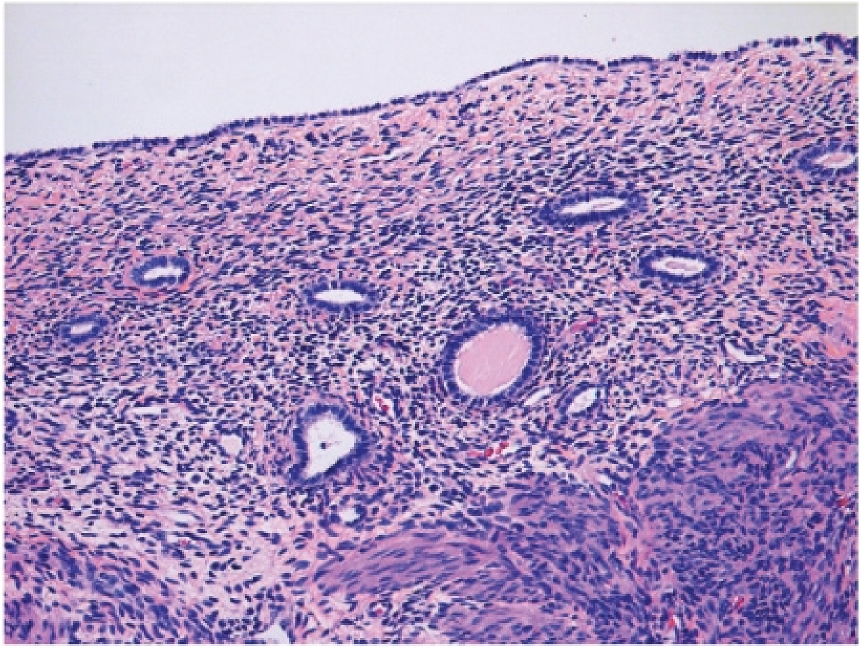
B Secretory

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



C Pregnancy

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



D Inactive

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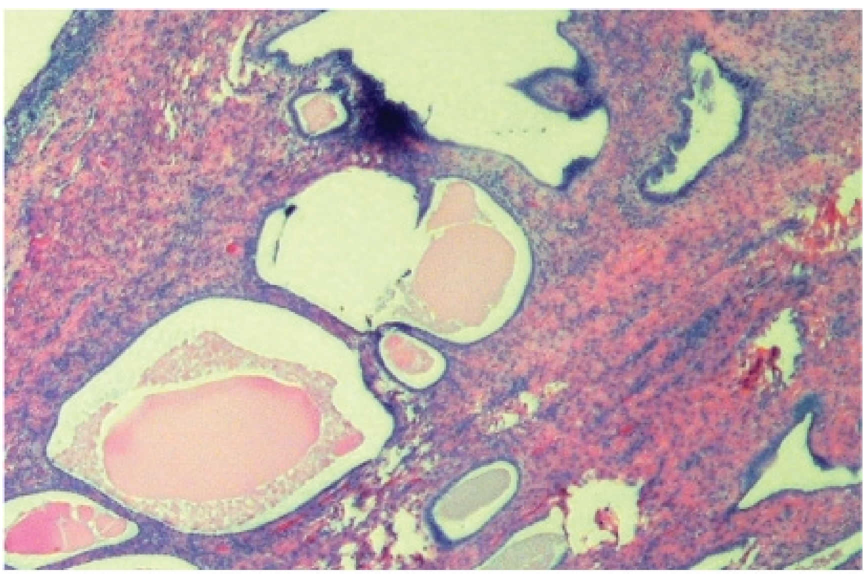


E Atrophic

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photographs of endometrial histologic specimens. **A.** In a proliferative endometrium, the glands are rounded and closely packed and have tall columnar epithelium with mitosis. **B.** Secretory endometrium shows tortuous glands lined by cells with cytoplasmic and luminal secretions. **C.** In pregnancy, these changes become more pronounced with a hypersecretory effect demonstrated by cell clearing and cytoplasmic blebs. **D.** Inactive endometrial tissue shows only scattered, inactive nonproliferating glands in the basalis. **E.** With endometrial atrophy, cystic changes can occur. *(Courtesy of Dr. Raheela Ashfaq).*

MENSTRUAL DISTURBANCES

Menses may be irregular in more than one half of all women during menopausal transition (Treloar, 1981). In all women, regardless of menopausal status, the etiology of abnormal bleeding should be determined (see Chap. 8). Anovulation is the most common cause of erratic bleeding during the transition, although endometrial hyperplasia, estrogen-sensitive neoplasms such as endometrial polyps and uterine leiomyomas, and pregnancy should always be considered. Many women in their 40s do not consider themselves fertile and will cease using contraception.

Endometrial cancer should be suspected in any woman in menopausal transition with abnormal uterine bleeding. The overall incidence of endometrial cancer is approximately 0.1 percent of women in this group per year, but in women with abnormal uterine bleeding, the risk increases to 10 percent (Lidor, 1986). Malignant precursors of endometrial cancer such as complex endometrial hyperplasia become more common during the menopausal transition, and early diagnosis with endometrial biopsy should be done to exclude malignancy (see Chap. 33, Endometrial Hyperplasia).

Although endometrial neoplasia is the greatest concern during this time, endometrial biopsy frequently reveals a non-neoplastic endometrium displaying estrogen effects unopposed by progesterone. In premenopausal women, this results from anovulation. In postmenopausal women, unopposed estrogen may be derived from extragonadal endogenous estrogen production, which may result from increased aromatization of androgen to estrogen due to obesity. In addition, decreased SHBG levels lead to increased levels of free, and therefore bioavailable, estrogen (Moen, 2004). Unopposed estrogen administration can also account for these effects in postmenopausal women.

EVALUATION OF ABNORMAL BLEEDING

Sonography

Transvaginal sonographic measurement of endometrial thickness can be used in postmenopausal women to avoid endometrial biopsy (see Chap. 2, Transvaginal Sonographic Endometrial Evaluation). Speroff (2005) recommends that in postmenopausal women with abnormal bleeding, endometrial biopsy is not required if the endometrial thickness is less than 5 mm, because the risk of endometrial hyperplasia or cancer is low. Evidence is lacking about the application of this criterion to premenopausal women. However, a biopsy is indicated in a premenopausal patient if a clinical history suggests long-term unopposed estrogen exposure, even if the endometrial thickness is "normal" (5 to 12 mm).

Endometrial Biopsy

The diagnostic approach to a woman in menopausal transition with abnormal bleeding has evolved over the last century from operating room dilatation and curettage (D&C), to outpatient vacuum-suction curettage, to eventually the Pipelle plastic catheter (see Fig. 8-5) (Stovall, 1991; Guido, 1995).

Less than 10 percent of postmenopausal women cannot be adequately evaluated by office biopsy. Inability to enter the uterine cavity is the most common reason for failure. In such instances, pretreatment with the prostaglandin E_1 analog misoprostol (Cytotec, Pharmacia, Morpeth, UK), 100 mg orally the night before and morning of biopsy, may be warranted. Misoprostol softens the cervix and typically allows passage of a Pipelle through a stenotic os. This may avert the need for forceful dilatation and curettage.

Hysteroscopy

Hysteroscopy is also useful to evaluate abnormal uterine bleeding. This tool allows for evaluation of focal intrauterine lesions and targeted biopsy of specific lesions such as submucous leiomyomas, endometrial polyps, or focal areas of endometrial hyperplasia or endometrial cancer (see Section 41-35, Hysteroscopy). Patients with a stenotic cervical os that does not allow an in-office endometrial biopsy to be performed can be pretreated with misoprostol 100 mg orally the night before and the morning of scheduled hysteroscopy, to ease cervical dilation.

Central Thermoregulation Changes

INCIDENCE

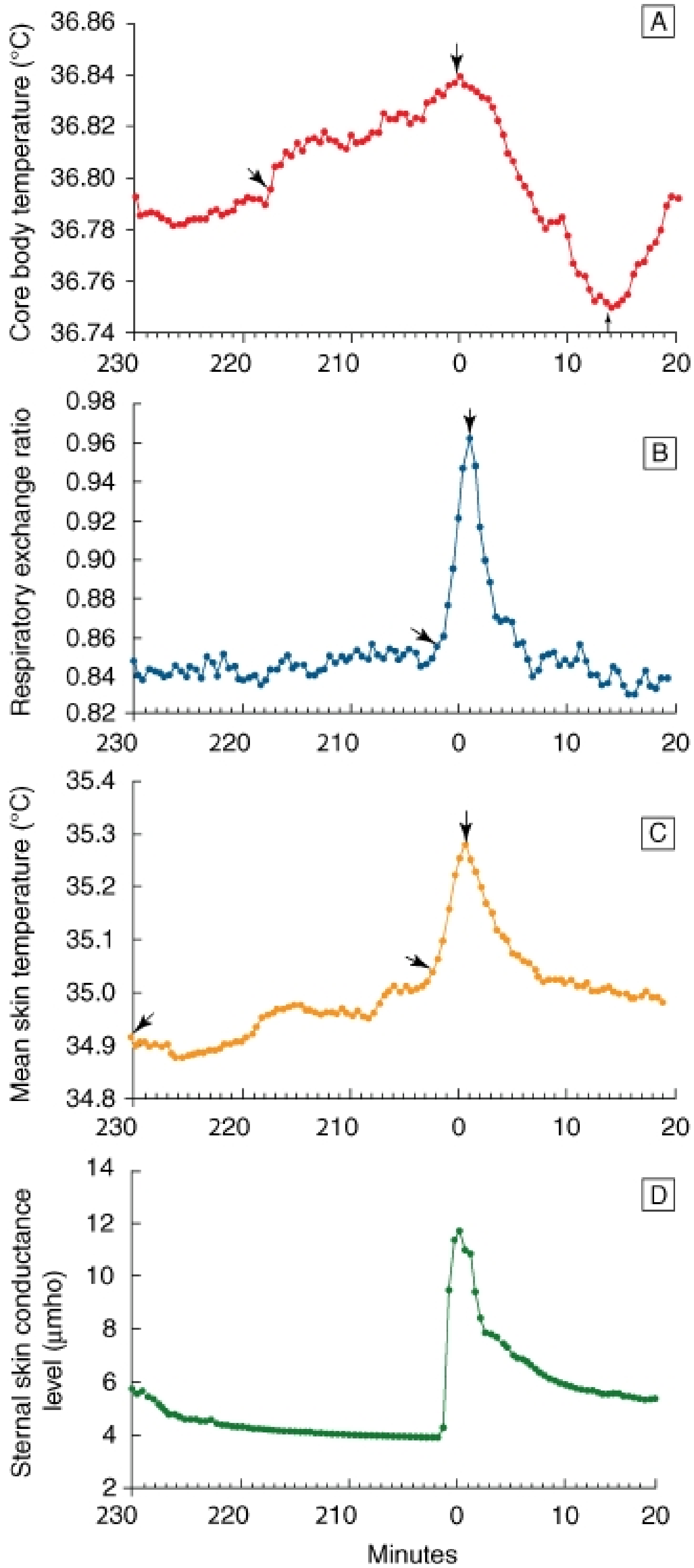
Vasomotor symptoms, which may be described as hot flashes, hot flushes, and night sweats, are the most common medical

complaint of women during menopausal transition. Kronenberg (1990) tabulated all of the published epidemiologic studies and determined that vasomotor symptoms developed in 11 to 60 percent of menstruating women during the transition. In the Massachusetts Women's Health Study, the incidence of hot flushes increased from 10 percent during the premenopausal period to approximately 50 percent after cessation of menses (McKinlay, 1992). Hot flushes begin an average of 2 years before the FMP, and 85 percent of women who experience them will continue to experience them for more than 1 year. Of these women, 25 to 50 percent will have hot flushes for 5 years, and 15 percent may experience them for >15 years (Kronenberg, 1990).

VASOMOTOR SYMPTOMS

Thermoregulatory and cardiovascular changes that accompany a hot flush have been well documented. An individual hot flush generally lasts 1 to 5 minutes, and skin temperatures rise because of peripheral vasodilation (Kronenberg, 1990). This change is particularly marked in the fingers and toes, where skin temperature can increase 10 to 15Â°C. Most women sense a sudden wave of heat that spreads over the body, particularly on the upper body and face. Sweating begins primarily on the upper body, and it corresponds closely in time with an increase in skin conductance (Fig. 21-5). Sweating has been observed in women during 90 percent of hot flushes (Freedman, 2001).

FIGURE 21-5



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Physiologic changes (means) during a hot flush. **A.** Core body temperature. **B.** Respiratory exchange ratio. **C.** Skin temperature. **D.** Sternal skin conductance. Time 0 is the beginning of the sternal skin conductance response. *(Redrawn from Freedman, 1998, with permission).*

Increases in both awake and sleep systolic blood pressure are noted with hot flushes (Gerber, 2007). In addition, heart rate increases 7 to 15 beats per minute at approximately the same time as peripheral vasodilatation and sweating. Heart rate and skin blood flow usually peak within 3 minutes of the onset of the hot flush. Simultaneously with sweating and peripheral vasodilation, the metabolic rate also significantly rises. Hot flushes may also be accompanied by palpitations, anxiety, irritability, and panic.

Five to 9 minutes after a hot flush begins, core temperature decreases 0.1 to 0.9Â°C due to heat loss from perspiration and increased peripheral vasodilation (Molnar, 1981). If the heat loss and sweating is significant, a woman may experience chills. Skin temperature gradually returns to normal, sometimes taking 30 minutes or longer.

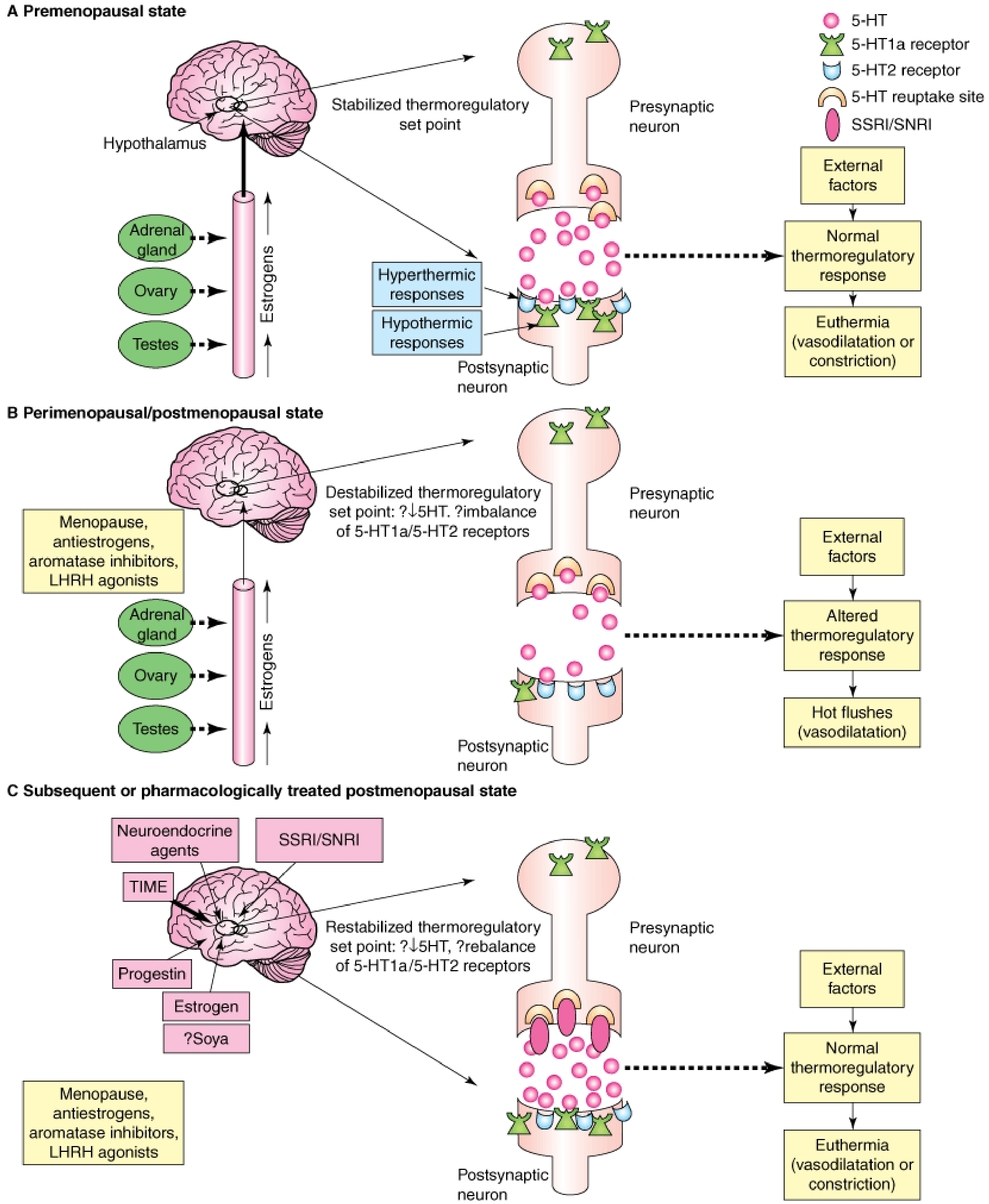
PATHOPHYSIOLOGY OF VASOMOTOR SYMPTOMS

Despite the prevalence and impact of hot flushes, the pathophysiology of vasomotor symptoms is not clearly understood (Bachmann, 2005). Some dysfunction of central thermoregulatory centers in the hypothalamus is likely the cause of this common symptom. The medial preoptic area of the hypothalamus contains the thermoregulatory nucleus responsible for regulating perspiration and vasodilatation, which is the primary mechanism of heat loss in humans. If exposed to temperature changes, this nucleus activates these heat dissipation mechanisms. These maintain core body temperature in a regulated normal range, called the *thermoregulatory zone* .

Estrogens

Certainly, estrogens play a vital role in the development of hot flushes (Fig. 21-6). Although there is no clear correlation between the two, estrogen withdrawal or rapid fluctuation in levels, rather than low estrogen concentration, is suspected (Erlik, 1982; Overlie, 2002). This hypothesis is supported by the fact that women with gonadal dysgenesis (Turner syndrome), who lack normal estrogen levels, do not experience hot flushes unless first exposed to estrogen and then withdrawn from treatment.

FIGURE 21-6



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Diagram of the interactions between sex steroid hormones and serotonin in the central nervous system (CNS) and their effects on thermoregulatory response. Serotonin (5-HT) receptors are those for the neurotransmitter serotonin **A.** Estrogen stabilizes the CNS thermoregulatory set point and leads to a normal response. **B.** During menopausal transition, decreased estrogen levels lead to instability of the set point and an altered response to external thermal stimuli. **C.** Gradually over time, the set point becomes stable again. Alternatively,

pharmacologic intervention with exogenous estrogen or selective serotonin reuptake inhibitors (SSRIs) may also stabilize the set point. 5-HT = 5-hydroxytryptamine; LHRH = luteinizing hormone-releasing hormone; SNRI = selective norepinephrine reuptake inhibitor. *(Redrawn from Stearns, 2002, with permission.)*

Neurotransmitters

Although estrogen withdrawal clearly has a significant impact on hot flush development, recent research has demonstrated that other factors are involved (Bachmann, 2005). For example, Freedman and colleagues (1998, 2001) hypothesized that changes in neurotransmitter levels may contribute to hot flushes. Altered neurotransmitter concentrations may create a narrow thermoregulatory zone and a lowered sweating threshold. Thus, even subtle changes in core body temperature may trigger heat loss mechanisms.

Norepinephrine

Norepinephrine is thought to be the primary neurotransmitter responsible for lowering the thermoregulatory setpoint and triggering the heat loss mechanisms associated with hot flushes (Rapkin, 2007). Plasma levels of norepinephrine metabolites are increased before and during hot flushes. Moreover, studies have shown that norepinephrine injections can increase core body temperature and induce a heat loss response (Freedman, 1990). Conversely, medications that decrease norepinephrine levels may reduce vasomotor symptoms (Laufer, 1982).

Estrogens are known to modulate adrenergic receptors in many tissues. Freedman and colleagues (2001) suggested that hypothalamic α_2 -adrenergic receptors are decreased by menopause-related decreases in estrogen levels. They showed that a decline in presynaptic α_2 -adrenergic receptors leads to increased norepinephrine levels, thereby causing vasomotor symptoms.

Serotonin

Serotonin is likely to be another neurotransmitter that is involved in the pathophysiology of hot flushes (Slopien, 2003). Estrogen withdrawal is associated with a decreased blood serotonin level, which is followed by upregulation of serotonin receptors in the hypothalamus. Activation of specific serotonin receptors has been shown to mediate heat loss (Gonzales, 1993). However, the role of serotonin in central regulatory pathways is complex because binding at some serotonin receptors can exert negative feedback on other serotonin receptor types (Bachman, 2005). Therefore, the effect of a change in serotonin activity depends on the type of receptor activated.

In sum, these and other studies suggest that reductions and significant fluctuations in estradiol levels lead to a decline in inhibitory presynaptic α_2 -adrenergic receptors and an increase in hypothalamic norepinephrine and serotonin release. Norepinephrine and serotonin lower the setpoint in the thermoregulatory nucleus and allows heat loss mechanisms to be triggered by subtle changes in core body temperature.

Sleep Dysfunction and Fatigue

Sleep disruption is a common complaint of women with hot flushes. Women may awake several times during the night and may be drenched in sweat. Disturbed sleep can lead to fatigue, irritability, depressive symptoms, cognitive dysfunction, and impairment in daily functioning.

The relationship between hot flushes and impaired sleep has been studied (Table 21-2). Hollander (2001) studied a cohort of late reproductive-aged women and found that women with a greater incidence of hot flushes were more likely to report poor sleep than were women with fewer vasomotor symptoms. Kravitz and colleagues (2003) found that the incidence and severity of sleep disorders appeared to be increased in late menopausal transition and at menopause, the periods during which women are most likely to experience vasomotor symptoms.

Table 21-2 Insomnia by Severity of Hot Flushes and Menopausal Symptoms						
	Insomnia Symptoms ≥ 6 mo					
Variable	**DIS**	**DMS**	**NRS**	**At Least 1 Symptom**	**GSD**	**DSM-IV Insomnia Diagnosis**
Hot flashes (%)						
None (n = 673)	7.7	30.5	6.8	12.9	36.0	10.5
Mild (n = 172)	11.6	47.1	15.1	15.1	52.9	23.3
Moderate (n = 89)	19.1	56.2	25.8	28.1	66.3	30.3
Severe (n = 48)	35.4[a]	68.8[a]	35.4[a]	52.1[a]	81.3[a]	43.8[a]
Menopausal status (%)						
Premenopause (n = 562)	9.4	30.2[a]	9.3	15.3	36.5	13.0
Perimenopause (n = 219)	16.0	49.8	20.1[a]	23.3	56.6[a]	26.0
Postmenopause (n = 201)	9.0	44.8	8.0	12.9	50.7	14.4

[a] $p < .001$

DIS = difficulty initiating sleep; DMS = difficulty maintaining sleep; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition;* GSD = global sleep dissatisfaction; NRS = nonrestorative sleep.

From Ohayon (2006), with permission.

Many women begin to have prolonged feelings of fatigue, exhaustion, and lack of energy during menopausal transition. Fatigue may be related to night sweats and difficulty sleeping or an independent risk factor that is yet to be identified. Common sense education for patients during menopausal transition may prove valuable (Table 21-3).

Table 21-3 Fatigue Prevention Instructions
Obtain adequate sleep every night
Exercise regularly to reduce stress
Avoid long work hours and maintain your personal schedule
If stress is environmental, take vacations, switch jobs, or approach your company or family to help resolve sources of your stress
Limit intake of alcohol, drugs, and nicotine
Eat a healthy and well-balanced diet
Drink adequate amounts water (8 to 10 glasses) during the early part of the day
Consider seeing a specialist in menopausal medicine

RISK FACTORS FOR VASOMOTOR SYMPTOMS

Several risk factors have been associated with an increased probability of hot flushes, including surgical menopause, race/ethnicity,

body mass, and smoking. Surgical menopause is associated with a 90-percent probability of hot flushes during the first year after oophorectomy, and symptoms can be more abrupt and severe than those associated with natural menopause. Research has also demonstrated that the prevalence of vasomotor symptoms varies among racial and ethnic groups. Hot flushes appear to be more common in African-American than in white women and are more common among white than among Asian women (Gold, 2001; Kuh, 1997).

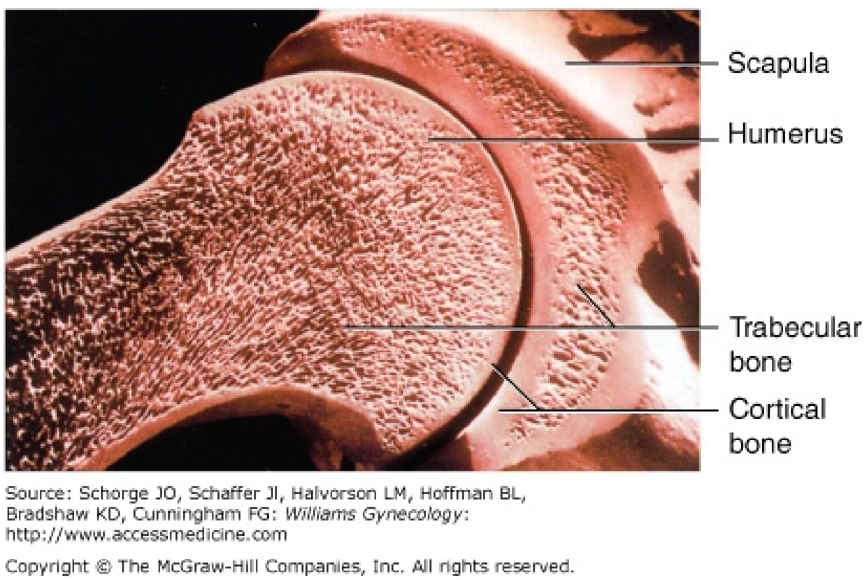
The impact of body mass on hot flush frequency is not clear. Some investigators have reported that thinner women are more likely to experience hot flushes, whereas others have found that heavier women are more commonly affected (Erlik, 1982; Wilbur, 1998). Other risk factors include early menopause, low circulating levels of estradiol, a sedentary lifestyle, smoking, and use of selective estrogen receptor modulators (SERMs) (Bachman, 2005). In addition, women exposed to high ambient temperatures may experience more frequent and severe hot flushes. Randolph (2005) found that the incidence of hot flushes at 31Â°C may be four times as great as that at 19Â°C. A thorough discussion of treatment options for hot flushes is found in Chapter 22, Treatment of Vasomotor Symptoms.

Bone Metabolism and Structural Changes

Normal bone is a dynamic, living tissue that is in a continuous process of destruction and rebuilding. This bone remodeling, also described as *bone turnover* , allows adaptation to mechanical changes in weight bearing and other physical activities.

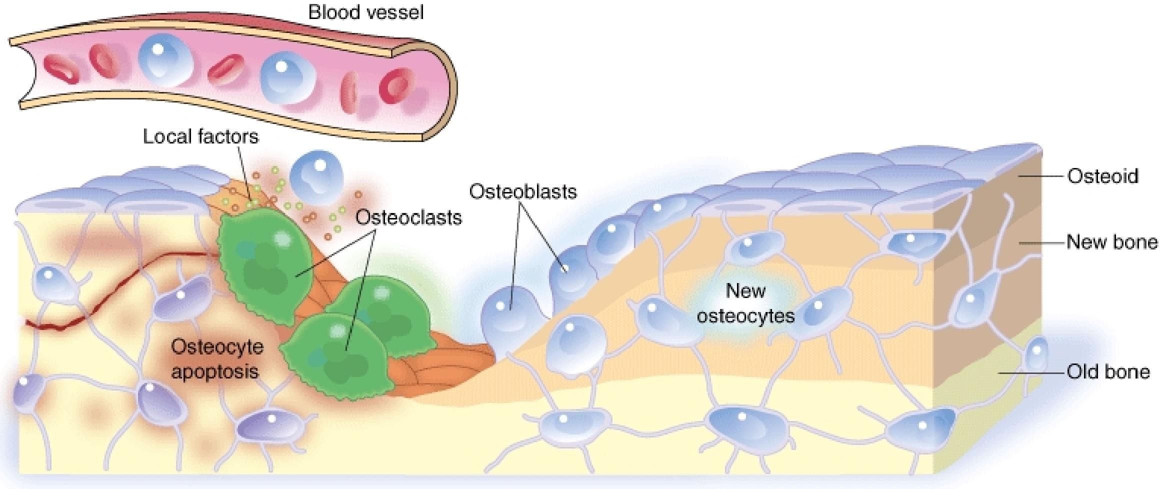
The skeleton consists of two bone types (Fig. 21-7). Cortical bone is the bone of the peripheral skeleton (arms and legs) and accounts for 80 percent of total bone. Trabecular bone is the bone of the axial skeleton, which includes the spinal column, pelvis, hip, and proximal femur. The process of bone remodeling involves a constant resorption of bone, carried out by multinucleated giant cells known as *osteoclasts* , and a concurrent process of bone formation, completed by *osteoblasts* (Fig. 21-8).

FIGURE 21-7



Photograph of bone with trabecular and cortical bone labeled. *(From Saladin, 2005, with permission).*

FIGURE 21-8



Bone remodeling. Osteoclasts resorb matrix, whereas osteoblasts deposit new lamellar bone. Osteoblasts that are trapped in the matrix become osteocytes. Others die or form new, flattened osteoblast lining cells. *(Redrawn from Seeman, 2006, with permission).*

Peak bone mass is influenced by heredity and endocrine factors, and there is only a relatively narrow window of opportunity for acquiring bone mass. Almost all bone mass in the hip and the vertebral bodies will be accumulated in young women by late adolescence, so the years immediately following menarche (ages 11 to 14 years) are especially important (Sabatier, 1996; Theintz, 1992). Following this peak, bone resorption is normally coupled to bone formation such that positive bone balance is achieved when skeletal maturity is attained, typically at ages 25 to 35 years.

Thereafter, bone mass declines at a slow, steady rate of about 0.4 percent each year. During menopause, the rate increases to 2 to 5 percent per year for the first 5 to 10 years and then slows to 1 percent per year. The subsequent risk of fracture from osteoporosis will depend on bone mass at the time of menopause and the rate of bone loss following menopause (Riis, 1996).

Osteopenia and Osteoporosis

INCIDENCE

These bone disorders are characterized by a progressive reduction in bone mass (typically greater in trabecular bone) and predispose patients to fractures in the spine, hips, and other sites. It is estimated that 7.8 million American women have osteoporosis and 21.8 million have low bone density in the hip.

OSTEOPOROSIS SEQUELAE

Fractures are the most debilitating and costly consequence of osteoporosis. Approximately 1.5 million Americans experience osteoporotic fractures each year. The spine, hip, and wrists are most commonly fractured (Kanis, 1994). Osteoporotic fractures are associated with significant morbidity and mortality, and the risk of dying following a clinical fracture is reportedly twofold higher than for persons without fractures. The overall mortality from hip fracture alone is estimated to be 30 percent. In addition, only 40 percent of those who sustain a hip fracture are capable of returning to their prefracture level of independence. Osteoporotic fractures are associated with high health care resource utilization and carry an economic burden in the United States of approximately 20 billion dollars annually (Kanis, 1994).

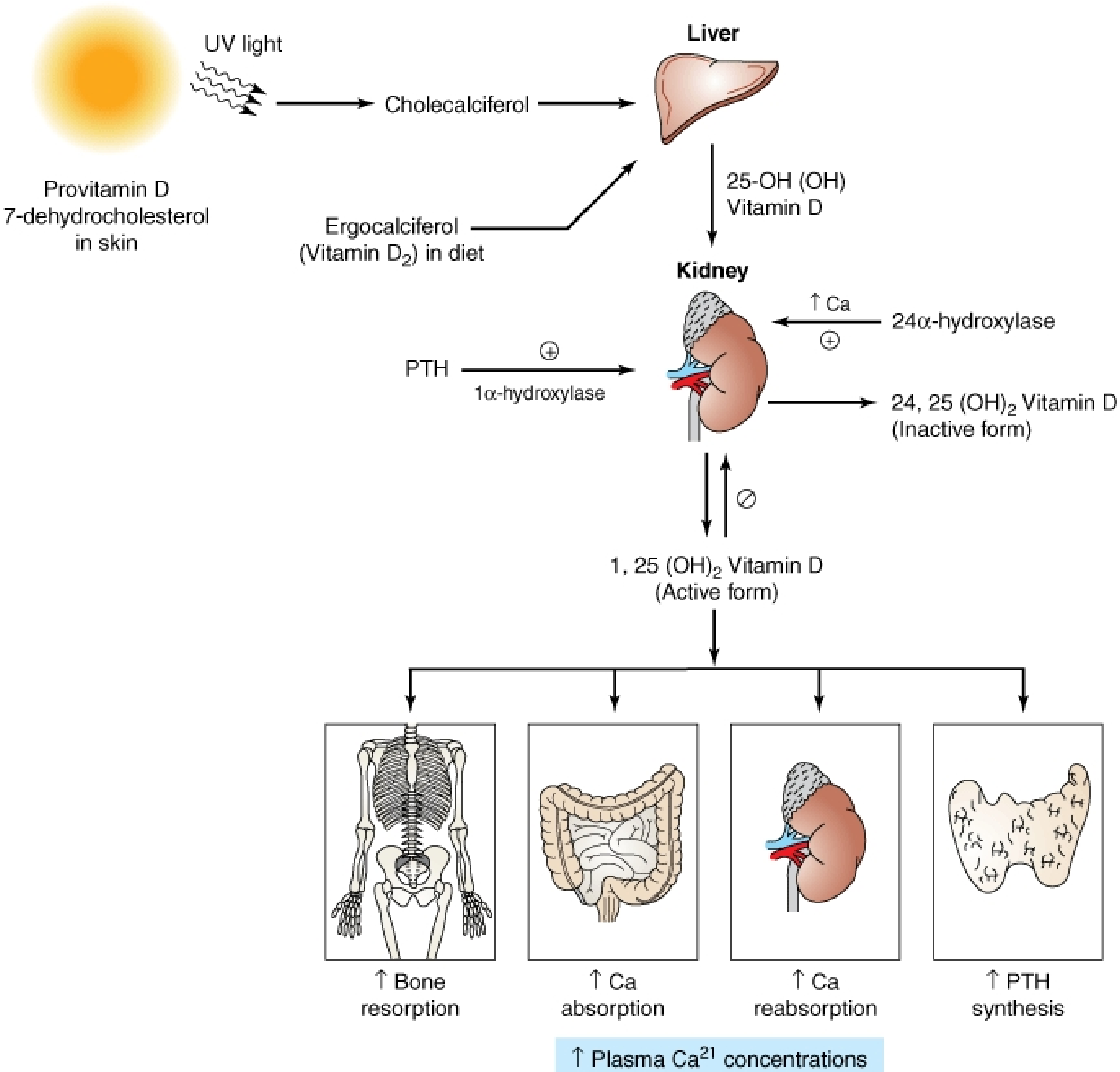
Pathophysiology

Osteoporosis is a skeletal disease in which bone strength is compromised, resulting in an increased risk for fracture. A major proportion of bone strength is determined by bone mineral density (BMD), which explains why BMD measurements are effective tools for identifying patients at high risk for fractures. However, bone strength and fracture risk are also affected by other qualities of bone such as rates of remodeling, size and geometry, microarchitecture, mineralization, damage accumulation, and matrix quality (Kiebzak, 2003).

Primary osteoporosis refers to bone loss associated with aging and menopausal estrogen deficiency. As its levels fall after menopause, estrogen's regulatory effect on bone resorption is lost. As a result, bone resorption is accelerated and is usually not balanced by compensatory bone formation. This accelerated bone loss is most rapid in the early postmenopausal years (Gallagher, 2002). If osteoporosis is caused by other diseases or medications, the term *secondary osteoporosis* is used (Stein, 2003).

The amount of bone at any point in time reflects the balance of the osteoblastic (building) and osteoclastic (resorbing) activities, which are influenced by a multitude of stimulating and inhibiting agents (Canalis, 2007). As noted above, both aging and a loss of estrogen lead to a significant increase in osteoclastic activity. In addition, a decrease in calcium intake or impaired absorption of calcium from the gut lowers the serum level of ionized calcium. This stimulates parathyroid hormone (PTH) secretion to mobilize calcium from bone by stimulation of osteoclastic activity (Fig. 21-9). Increased PTH levels stimulate the production of vitamin D. In turn, increases in vitamin D lead to increased serum calcium levels by several effects: (1) stimulates osteoclasts to remove calcium from bone, (2) increases intestinal calcium absorption, (3) stimulates renal calcium reabsorption (Holick, 2007).

FIGURE 21-9



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Vitamin D metabolism. Provitamin D (7-dehydrocholesterol) in the skin is converted to cholecalciferol by ultraviolet (UV) light. Cholecalciferol and ergocalciferol (from plants) are transported to the liver, where they undergo hydroxylation to form the major circulating form of vitamin D. A second hydroxylation step occurs in the kidney and results in the hormonally active vitamin D [$1{,}25(OH)_2 D_3$], also known as calcitriol. This activation step is mediated by 1α-hydroxylase and is regulated by parathyroid hormone (PTH), Ca^{2+} levels, and vitamin D [$1{,}25(OH)_2 D_3$]. The activity of 1α -hydroxylase is stimulated by PTH and inhibited by Ca^{2+} and $1{,}25(OH)_2 D_3$. Vitamin D increases bone resorption, Ca^{2+} absorption from the intestine, renal Ca^{2+} reabsorption, and PTH production by the parathyroid glands. The overall effect of vitamin D is to increase plasma Ca^{2+} concentrations. *(From Molina, 2006, with permission).*

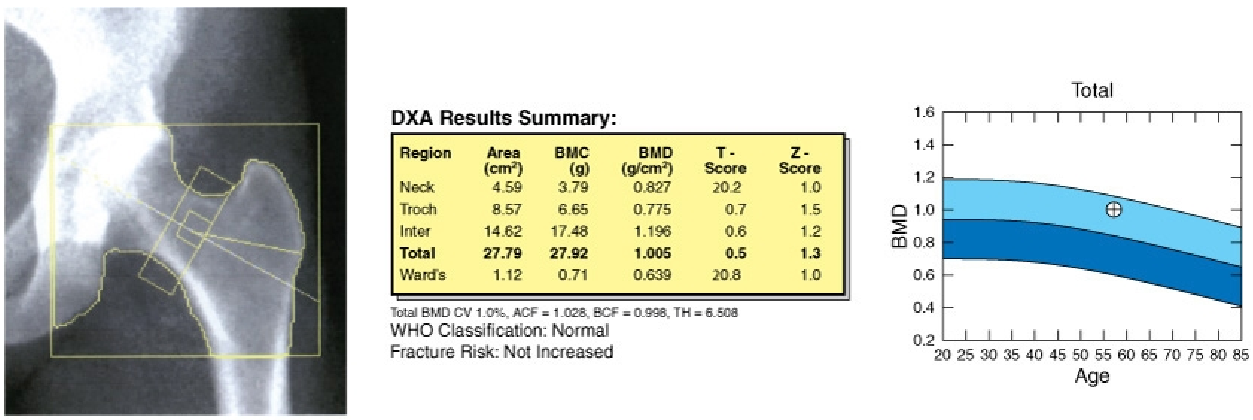
In normal premenopausal women, this series of events leads to increased serum calcium levels, and PTH levels return to normal. In menopausal women, estrogen deficiency leads to a greater responsiveness of bone to PTH. Thus, for any given level of PTH, there is more calcium removed from bone. This condition raises the level of serum calcium, which in turn lowers the level of PTH and

decreases the vitamin D level.

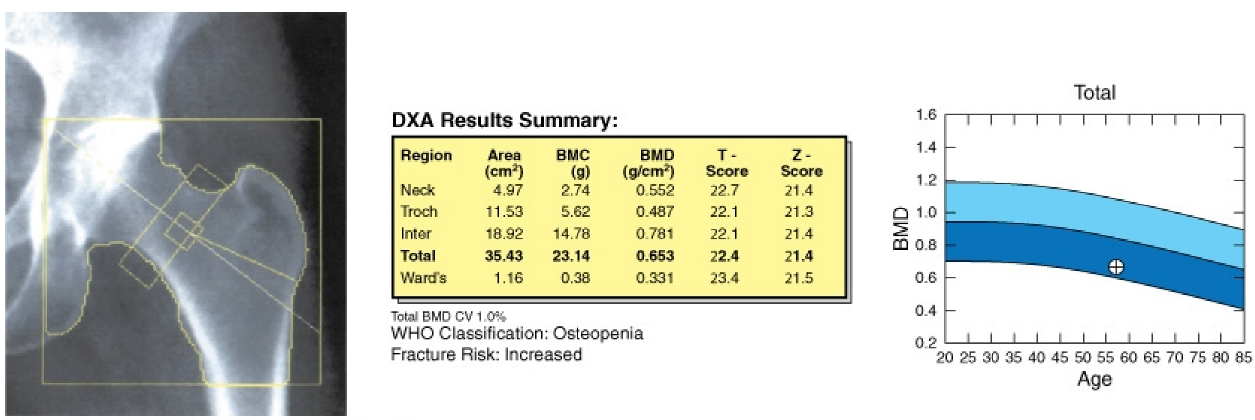
DIAGNOSIS OF OSTEOPOROSIS

Bone mineral density (BMD) is the standard used for bone mass determination and is commonly assessed with dual-energy x-ray absorptiometry (DEXA) of the lumbar spine, radius, and hip (Fig. 21-10) (Marshall, 1996). The lumbar spine contains primarily trabecular bone, which comprises 20 percent of the skeleton. This bone is less dense than cortical bone and has a faster bone remodeling rate. Therefore, early rapid bone loss can be determined by evaluation of this site. Cortical bone is denser and more compact bone and comprises 80 percent of bone. It is most abundant in the long-bone shafts of the appendicular skeleton. The greater trochanter and femoral neck contain both cortical and trabecular bone, and these sites are ideal for the prediction of hip fracture risk in older women (Miller, 2002).

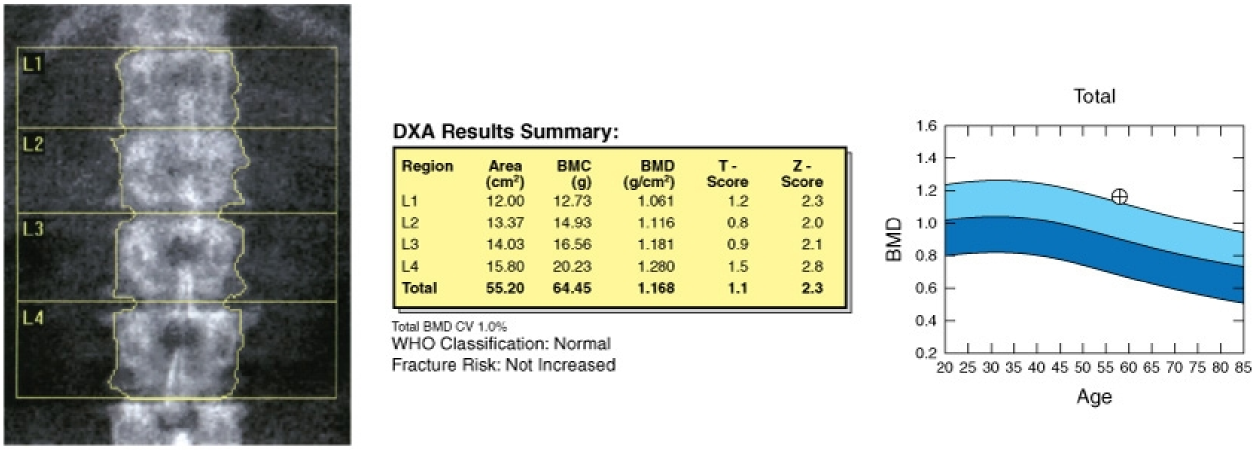
FIGURE 21-10



A

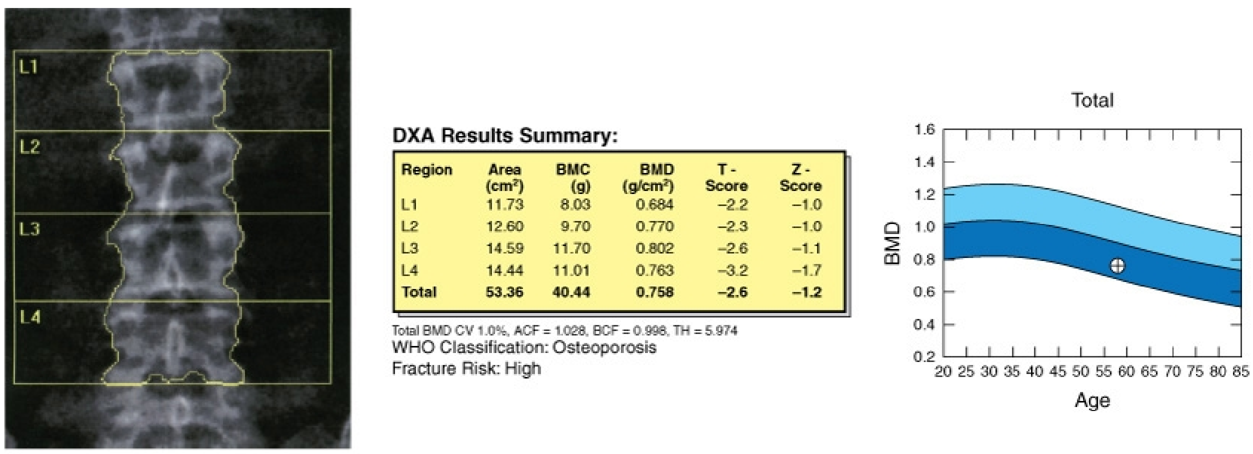


B



C

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



D

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Dual-energy x-ray absorptiometry (DEXA) scans. **A.** DEXA report describing normal hip density. **B.** DEXA report describing osteopenia of the hip. **C.** DEXA report describing normal vertebral body density. **D.** DEXA report describing vertebral body osteoporosis. BMC = bone mineral content; BMD = bone mineral density.

Normative bone mineral density values for sex, age, and ethnicity have been determined. For diagnostic purposes, results of BMD testing should be reported as *T-scores.* These measure in standard deviations (SDs) the variance of an individual's BMD from that expected for a person of the same sex at peak bone mass (25 to 30 years). A T-score of â€"2.0 in a woman, for example, means that her BMD is two SDs below the average peak bone mass for a young woman. Definitions from the National Osteoporosis Foundation include those found in Table 21-4. A fourth category "severe osteoporosis" has been suggested to describe patients who have a T-score below â€"2.5 and who have also suffered a fragility fracture. These are fractures caused by a fall from standing height or lower.

Table 21-4 Criteria for Interpretation of Bone Mineral Density

- Normal BMD is defined as a T-score between +2.5 and â€“1.0. The patient's BMD lies between 2.5 standard deviations (SDs) above the young adult mean and 1 SD below the young adult mean.
- Osteopenia (low BMD) is associated with a T-score between â€“1.0 and â€“2.5, inclusive. Osteopenia is also a term used by radiologists to indicate that bones on a radiograph appear to be of decreased mineral content.
- Osteoporosis is defined as a T-score lower than â€“2.5.

From the National Osteoporosis Foundation, 2003.

Patients will also be assigned a *Z-score,* which is the standard deviation between the patient's measurement and average bone mass for a patient with the same age and weight. Z-scores lower than â€“2.0 (2.5 percent of the normal population of the same age) require diagnostic evaluation for secondary osteoporosis, which includes causes other than menopausal bone loss (Faulkner, 1999). Similarly, any patient with osteoporosis should be screened for other conditions that lead to osteoporosis (Table 21-5).

Table 21-5 Secondary Causes of Osteoporosis and Recommended Testing

- Primary hyperparathyroidism: serum levels of parathyroid hormone, calcium, phosphorus, and alkaline phosphatase
- Secondary hyperparathyroidism from chronic renal failure: renal function tests
- Hyperthyroidism or excess thyroid hormone treatment: thyroid function tests
- Increased calcium excretion: 24-hour urine collection for calcium and creatinine concentrations
- Hypercortisolism, alcohol abuse, and metastatic cancer: careful history and when indicated appropriate laboratory studies
- Osteomalacia: serum levels of calcium, phosphorus, alkaline phosphatase, and 1,25-dihydroxyvitamin D

The relation between BMD and fracture risk has been calculated in a large number of studies. A meta-analysis by Marshall and colleagues (1996) showed that BMD is still the most readily quantifiable predictor of fracture risk for those who have not yet suffered a fragility fracture. For each standard deviation of BMD below a baseline level (either mean peak bone mass or mean for the reference population of the person's age and sex), the fracture risk approximately doubles (National Osteoporosis Foundation, 2003).

PREVENTION

Many factors have been suggested as predictors of risk of osteoporotic fractures (Table 21-6). The most important predictive factors are bone density in combination with age, fracture history, ethnicity, various drug treatments, weight loss, and physical fitness. The presence of a key risk factor should alert a clinician to the need for further assessment and possibly active intervention, such as calcium therapy coupled with weight-bearing exercise or pharmacologic therapy. Treatment options for osteoporosis are discussed in Chapter 22, Treatment of Osteoporosis.

Table 21-6 Osteoporosis Risk Factors	
Major Risk Factors	**Minor Risk Factors**
Age >65 years	Rheumatoid arthritis
Vertebral compression fracture	Prior history of clinical hyperthyroidism
Fragility fracture after age 40	Chronic anticonvulsant therapy
Family history of osteoporotic fracture	Low dietary calcium intake
Systemic glucocorticoid therapy of >3 months duration	Smoker
Malabsorption syndrome	Excessive alcohol intake
Primary hyperparathyroidism	Excessive caffeine intake
Propensity to fall	Weight <57 kg
Osteopenia apparent on radiography	>10 percent weight loss at age 25
Hypogonadism	Chronic heparin therapy
Early menopause (before age 45)	

Bone Mineral Density

This characteristic of bone is currently the best quantifiable predictor of osteoporotic fracture. Low BMD and other major risk factors combine to further increase a person's risk of fracture (National Osteoporosis Foundation, 2003). Therefore, BMD should be measured in a postmenopausal woman older than 50 years with one of the other major risk factors for fracture or in any woman older than 65.

Risk factors for osteoporotic fracture are not independent of one another. They are additive and must be considered in the context of baseline age and sex-related risks of fracture. For example, a 55-year-old woman with low BMD is at significantly less risk than a 75-year-old woman with the same low BMD. Similarly, a woman with low BMD and a prior fragility fracture is at considerably greater risk than another person with the same low BMD and no prior fracture.

Osteoporotic fractures occur most commonly in men and women older than 65 years. Medical interventions have only been demonstrated to be effective in preventing fractures in populations with an average age older than 65 years. However, most currently approved osteoporosis therapies prevent or reverse bone loss if initiated at, or soon after, the age of 50 years. Therefore, it seems prudent to begin the identification of people at high risk for osteoporosis in their 50s.

Fragility Fracture

As stated earlier, a prior fragility fracture places a person at increased risk for another fracture. The increased risk is 1.5- to 9.5-fold depending on age at assessment, number of prior fractures, and site of the incident fracture (Melton, 1999). Vertebral fractures have been best studied in this regard. The presence of a vertebral fracture increases the risk of a second vertebral fracture at least fourfold. A study of a placebo group in a major clinical trial showed that 20 percent of those who experienced a vertebral fracture during the period of observation had a second vertebral fracture within 1 year (Lindsay, 2001). Vertebral fractures are also indicators of increased risk of fragility fractures at other sites, such as the hip. Similarly, wrist fractures predict vertebral and hip fractures.

Aging

Age is clearly a major contributor to fracture risk. As summarized in a review by Kanis and others (2001) the 10-year probability of experiencing a fracture of forearm, humerus, spine, or hip increases as much as eightfold between ages 45 and 85 years for women.

Race

Osteoporosis is most common in menopausal white women, and in 2003 the National Osteoporosis Foundation found that 20 percent of these women have osteoporosis and 52 percent have low bone density. Although persons of any ethnicity can develop osteoporosis, data from the Third National Health and Nutrition Examination Survey (NHANES III) indicate that the risk is highest among non-Hispanic white and Asian women and lowest among non-Hispanic black women.

Genetics

Genetic influence on osteoporosis and BMD is extremely important. It has been estimated that heredity accounts for 50 to 80 percent of BMD variability (Ralston, 2002). These influences have been the subject of major scientific investigations, and a number of genes have been associated with osteoporosis. These discoveries, however, have yet to result in a clinical application. A family history of osteoporotic fracture has been best studied with respect to hip fracture. The Study of Osteoporotic Fractures, for example, identified a maternal history of hip fracture as a key risk factor for hip fracture in a population of elderly women (Cummings, 1995). In addition, a history of hip fracture in a maternal grandmother also carries an increased risk of this fracture.

Fall Precautions

Fractures are frequently associated with falls. Therefore, a history of falls or factors that increase rates of these accidents should be included in a risk assessment. Factors include those associated with general frailty, such as reduced muscle strength (inability to rise from a chair without assistance), impaired balance, low body mass, and reduced visual acuity (World Health Organization, 1994). Alcohol use and excessive use of sedative prescription drugs are also an important risks for falls.

Systemic Glucocorticoids

Therapy with glucocorticoids lasting more than 2 to 3 months is a major risk factor for bone loss and fracture, particularly among postmenopausal women and men older than 50 years. Most reviews and guidelines describe a daily dose of prednisone that is ≥ 7.5 mg as the threshold for assessment and clinical intervention to prevent or treat glucocorticoid-induced osteoporosis (Canalis, 1996).

Screening

As a result of these risk factors, programs to confirm osteoporosis and determine disease severity should include BMD measurements in all menopausal women who: (1) are aged 65 years or older, (2) have one or more risk factors for osteoporosis, or (3) sustain fractures. If therapy to increase bone mineral density is instituted, density should be monitored.

Prophylaxis for osteoporosis with weight-bearing exercise and calcium intake should begin in adolescence (Recker, 1992). Calcium supplementation in prepubertal and pubertal girls improves bone accrual, an important effect that should have long-lasting beneficial consequences (Bonjour, 2001; Rozen, 2003; Stear, 2003).

Cardiovascular Changes

CARDIOVASCULAR DISEASE RISK

Cardiovascular disease (CVD), including coronary heart disease, congestive heart failure, and stroke, is the leading cause of death in both men and women (Minino, 2002). Most cardiovascular disease develops from atherosclerotic changes in the major blood vessels. Risk factors are the same for men and women and include family history of cardiovascular disease, hypertension, smoking, diabetes mellitus, abnormal cholesterol/lipoprotein profile, and obesity. Age alone is a significant predictor of CVD risk in men and women.

Before menopause, women have a much lower risk for cardiovascular events compared with men their age. Reasons for protection from CVD in premenopausal women are complex, but a significant contribution can be assigned to the greater high-density lipoprotein (HDL) levels in younger women, which is an effect of estrogen. However, after menopause this benefit disappears over

time such that a 70-year-old woman begins to have a risk identical to that of a male of comparable age (Matthews, 1989). The risk of CVD increases exponentially for women as they enter menopause and estrogen levels decline (Matthews, 1994; van Beresteijn, 1993). This becomes vitally important for women in menopausal transition, when preventive measures can significantly improve both the quality and the quantity of their lives (see Chap. 1, Cardiovascular Disease). Statistics indicate that one in three women older than 65 years has some evidence of CVD. By age 55, 20 percent of all deaths are caused by CVD, and 30 to 40 percent of women eventually die of CVD.

The relationship between menopause and CVD incidence was first examined in the Framingham cohort of 2,873 women (Kannel, 1987). There was a trend for a two- to sixfold higher incidence of CVD in postmenopausal women compared with premenopausal women in the same age range. This pattern is similar to that seen with the incidence of osteoporosis, which increases dramatically during menopausal transition. Moreover, the increases in CVD associated with the menopausal transition are observed regardless of the age at menopause. These and other data indicate that withdrawal of estrogen may be associated with an increased risk of CVD.

CARDIOVASCULAR DISEASE PREVENTION

Importantly, clinicians should offer strategies to their postmenopausal patients that help to prevent or delay the onset of CVD. Since recent data have questioned the widespread prescription of hormones to avert this common problem, other strategies must be considered (see Chap. 22). As a part of the Women's Health Initiative (WHI), an observational study of women's activity levels, was conducted. Manson and colleagues (2002) identified the cardiovascular benefits of physical activity. They determined that walkingâ€”as well as vigorous exerciseâ€”prevented cardiovascular events in postmenopausal women regardless of their age, body mass index (BMI), or ethnic background. As expected, a sedentary lifestyle correlated directly with an increase in the risk for a coronary event (McKechnie, 2001).

Central adiposity is a risk factor for coronary heart disease in women and is associated with a relatively androgenic hormonal state (see Fig. 17-8). Central fat distribution, also termed truncal obesity, in women is positively correlated with increases in total cholesterol, triglyceride, and LDL levels, and negatively correlated with HDL levels (Haarbo, 1989). This atherogenic lipid profile associated with abdominal adiposity is at least partly mediated through interplay with insulin and estrogen. A strong correlation exists between the magnitude of the worsening in cardiovascular risk factors (lipid and lipoprotein changes, blood pressure, and insulin levels) and the amount of weight gained during the menopausal transition (Wing, 1991). Davies (2001) and Matthews (2001) have shown that weight gain at menopause is not an effect of hormonal changes, but rather reflects diet, exercise, and a reduction of metabolic rate associated with aging.

Lipids

Physiologic levels of estrogen are known to help maintain favorable lipoprotein profiles in women. Specifically, throughout adulthood HDL levels are approximately 10 mg/dL higher in women, and this difference continues throughout the postmenopausal years. Moreover, total cholesterol and low-density lipoprotein (LDL) levels are lower in premenopausal women than in men (Jensen, 1990; Matthews, 1989). After menopause and with the subsequent decrease in estrogen, this favorable effect on lipids is lost. High-density lipoprotein levels decrease and total cholesterol levels increase.

After menopause, the risk of coronary heart disease doubles for women and at approximately age 60, the atherogenic lipids reach levels higher than those in men. Brunner (1987) and Jacobs (1990), each with their colleagues, have prospectively documented the strong association between total cholesterol and coronary heart disease in women, however, coronary heart disease risk appears at higher total cholesterol levels for women than for men. Women with a total cholesterol concentration greater than 265 mg/dL have rates of coronary heart disease three times those of women with low or normal levels. A low HDL-cholesterol level is also a strong predictor of CVD in women. The average HDL cholesterol in women is 55 to 60 mg/dL and a decrease in HDL cholesterol of 10 mg/dL increases coronary heart disease risk by 40 to 50 percent (Kannel, 1987).

Despite these changes in atherogenic lipids following menopause, total cholesterol and LDL levels can be favorably reduced by dietary modifications, estrogen treatment, and lipid-lowering medications (Matthews, 1994).

Coagulation

Changes in clotting parameters are known to occur with aging. Fibrinogen, plasminogen activator inhibitor-1, and factor VII

increase and cause a relatively hypercoagulable state. This is thought to contribute to increases in cardiovascular and cerebrovascular disease in older women.

Weight Gain and Fat Distribution

Weight gain is a common complaint among women in the menopausal transition. With aging, a woman's metabolism slows, reducing her caloric requirements. If eating and exercise habits are not altered, weight is gained (Matthews, 2001). Specifically, Espeland and colleagues (1997) characterized the weight and fat distribution of 875 women in the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial and correlated the impact of lifestyle, clinical, and demographic factors. They found that women aged 45 to 54 years had significantly greater increases in weight and in hip circumference than those aged 55 to 65 years. Reported that overall baseline physical activity and baseline leisure and work activities were strongly related to weight gain in the PEPI cohort. Women who reported more activity gained less weight than less active women.

Weight gain during this period is associated with fat deposition in the abdomen, which increases the likelihood of developing insulin resistance and subsequent diabetes mellitus and heart disease (Dallman, 2004; Wing, 1991). In addition, as reviewed by Baumgartner (1995), data from the Rosetta Study and the New Mexico Aging Process Study show that older adults have higher percentages of body fat than younger adults at any age due to the loss of muscle mass with aging.

Numerous other factors underlie weight gain and include genetic factors, neuropeptides, and adrenergic nervous system activity (Milewicz, 1996). Although many women believe that noncontraceptive estrogen therapy causes weight gain, recent results from clinical trials and epidemiologic studies indicate that the impact of menopausal hormone therapy on body weight and girth, if any, is to decrease slightly the rate of age-related increases.

Dermatologic Changes

Skin changes that may occur in the menopausal transition include hyperpigmentation (age spots), wrinkles, and itching. These are caused in part from skin aging, which results from the synergistic effects of intrinsic aging and photo-aging (Guinot, 2005). In addition, hormonal aging of the skin is thought to be responsible for many dermal changes. These changes include a reduced thickness due to reduced collagen content, a decrease in sebaceous gland secretion, a loss of elasticity, diminished blood supply, and epidermal changes (Wines, 2001).

Although the impact of hormone deficiency on skin aging has been widely studied, its distinction from the effects of intrinsic aging, photo-aging, and other environmental insults is difficult.

Dental Changes

Dental problems may also develop as estrogen levels wane in late menopausal transition. The buccal epithelium undergoes atrophy due to estrogen deprivation, resulting in decreased saliva and sensation. A bad taste in the mouth, increased incidence of cavities, and tooth loss also may occur (Krall, 1994).

Oral alveolar bone loss is strongly correlated with osteoporosis and can lead to tooth loss. The beneficial effect of estrogen on skeletal bone mass is also manifested on oral bone. Even in women without osteoporosis, there is a correlation between spinal bone density and number of teeth. Tooth loss is also strongly correlated with the use of cigarettes and the adverse effect they have on dental health (Krall, 1994).

Breast Changes

The breast undergoes change during menopause mainly because of hormonal withdrawal. In premenopausal women, estrogen and progesterone exert proliferative effects on ductal and glandular structures, respectively. At menopause, withdrawal of estrogen and progesterone leads to a relative reduction in breast proliferation. A significant reduction in the volume and percentage of dense tissue on mammography is noted, and these areas become replaced with adipose tissue.

Central Nervous System

SLEEP DYSFUNCTION

Difficulties in sleep onset and sleep maintenance are common in menopausal women. Sleep fragmentation is commonly associated

with hot flushes and results in daytime fatigue, mood lability, irritability, and problems with short-term memory (Owens, 1998). Even women with few vasomotor symptoms may experience insomnia and associated menopause-related mood symptoms (Erlik, 1982; Woodward, 1994). At times, short-term use of pharmacologic sleep aids are indicated, and these are listed in Table 1-21.

As women age, they are more likely to experience lighter sleep and are awakened more easily by pain, sound, or bodily urges. Health issues and other chronic conditions experienced by women, or not infrequently their spouse or bedmate, are likely to further disrupt sleep. Arthritis, carpal tunnel syndrome and other painful conditions, chronic lung disease, heartburn, and certain medications that are known to disrupt sleep may have a dramatic impact on quality and quantity of restful sleep. Nocturia, urinary frequency, and urgency, all of which are more common in menopausal women, are also important factors.

Sleep disordered breathing (SDB), which includes various degrees of pharyngeal obstruction, is much more common in menopausal women and their mates. In women, SDB is commonly associated with increased body mass and declining estrogen and progesterone levels. Loud snoring may develop due to upper airway obstruction and can range in severity from upper airway resistance to obstructive sleep apnea (Gislason, 1993). In all these examples, treatment of underlying heath conditions should be the focus to improve patient sleep.

COGNITIVE DYSFUNCTION

Memory decreases with advancing age. Although no direct effect of lowered estrogen levels on memory and cognition has been determined, many investigators suspect a relationship to, or an acceleration of, cognitive decline during menopause. Cognitive functioning was assessed in a cohort study of reproductive-aged and postmenopausal women not using hormone replacement therapy. In postmenopausal patients, cognitive performance declined with advancing age. This was not the case for reproductive-aged women. Premenopausal women in their forties were less likely to exhibit cognitive decline compared with postmenopausal patients in the same decade of life. These investigators concluded that there is accelerated deterioration of some forms of cognitive function after menopause (Halbreich, 1995).

Factors accelerating cerebral degenerative changes represent potentially modifiable risks for cognitive decline (Kuller, 2003; Meyer, 1999). Investigators have studied putative risk factors that accelerate subtle cognitive decline and dementia. They have correlated them with repeated measures of cerebral atrophy, computed tomography (CT) densitometry, and cognitive testing among neurologically and cognitively normal, aging volunteers. Risk factors for decreased cerebral perfusion and thinning of gray and white matter densities include transient ischemic attacks (TIAs), hyperlipidemia, hypertension, smoking, excess alcohol consumption, and male gender, which would imply lack of estrogen. The authors suggested interventions to control those risk factors amenable to modification.

Psychosocial Changes

Few studies of women's health in the menopausal years have formally assessed well-being and the psychosocial aspects of menopausal transition. Dennerstein and colleagues (1994) studied women during midlife to determine whether menopausal status, social circumstance, health status, interpersonal stress, attitude, and lifestyle behavior correlated with well-being in midlife. These investigators found that menopausal status had little effect on well-being. However, well-being was found to be significantly related to current perceived health status, general psychosomatic symptoms, general respiratory symptoms, history of premenstrual symptoms, and interpersonal stress. Attitudes toward aging and menopause were also significantly associated with well-being scores. Other investigators have found that psychosocial issues are common during this time, and do relate them directly to the fluctuation in hormonal levels.

Psychological and cognitive symptoms may develop during menopausal transition and include depression, mood changes, poor concentration, and impaired memory. Although many women perceive these changes as age-related aggravations or attribute them to worsening premenstrual syndrome (PMS), these symptoms may in fact result from changes in reproductive hormones (Bachmann, 1994; Schmidt, 1991).

More importantly, the menopausal transition is a complex sociocultural as well as a hormonal event. Psychosocial factors also may contribute to mood and cognitive symptoms during this phase, since women entering menopausal transition may face additional emotional stress from dealing with adolescents, onset of a major illness, caring for an aging parent, divorce or widowhood, career

change, or retirement (LeBoeuf, 1996).

Lock (1991) suggests that part of the stress reported by Western women is clearly culture-specific. Western culture emphasizes beauty and youth, and as women grow older, some suffer from a perceived loss of status, function, and control (LeBoeuf, 1996). However, the end of predictable menstruation and the end of fertility may be important to a woman simply because it is a change, no matter how aging and the end of reproductive life are viewed by that woman and by her culture (Frackiewicz, 2000). For some women, the approach of menopause may also be perceived as a significant loss, both to women who have accepted childbearing and rearing as their major life roles and those who are childless, perhaps not by choice. For these reasons, impending menopause may be perceived as a time of loss, when depression and other psychological disorders may develop (Avis, 2000).

Contemporary findings have dispelled myths that natural menopause, itself, is associated with depressed mood (Ballinger, 1990; Busch, 1994). That said, in general, there is a high percentage of subjects with recurrent depression at menopause, and a high percentage experiencing their first episode of depression during menopausal transition (Freeman, 2007; Spinelli, 2005).

It has been suggested that the hormonal fluctuations during early menopausal transition are responsible, in part, for this affective instability. Similarly, surgical menopause induces mood changes because of the rapid hormonal loss at this time. Soares (2005) hypothesizes that a major component of the reported emotional distress during menopausal transition may be causally related to high and erratic estradiol levels. For example, Ballinger and colleagues (1990) have shown that increases in stress hormones (and probably symptoms that are stress related) are physiologically linked with high estrogen levels. They also showed that women who had abnormal scores on psychometric tests early after menopause had higher estradiol levels than those with lower scores. In prospective, physiological studies of women reporting severe PMS, Spinelli and associates (2005) have shown that estrogen levels are correlated with the intensity of menopausal symptoms. A randomized, placebo-controlled menopause treatment study evaluated administered standard doses of conjugated equine estrogen (0.625 mg/d), which significantly improved sleep, but also showed an estrogen-related increase of inward-directed hostility (Schiff, 1980).

Libido Changes

Although the relationship between circulating hormones and libido has been extensively investigated, definitive data are lacking. Many studies demonstrate that other factors besides menopause may account for changes in libido (Gracia, 2007). Avis and colleagues (2000) studied sexual function in a subgroup of 200 women in the Massachusetts Women's Health Study II who underwent natural menopause. None took hormone treatment, and all these women had sexual partners. Menopausal status was observed to be significantly related to decreased sexual interest. However, after adjustment for physical and mental health, smoking, and marital satisfaction, menopause status no longer had a significant relationship to libido. Dennerstein (2005) prospectively evaluated 438 Australian women during 6 years of their menopausal transition. Menopause was significantly associated with dyspareunia and indirectly with sexual response. Psychological factors of feelings for one's partner, stress, and other social factors also indirectly affected sexual functioning.

Other investigators have demonstrated that sexual problems are more prevalent after menopause. A longitudinal study of women during the menopausal transition until at least 1 year after the final menstrual period demonstrated a significant decrease in the rate of weekly coitus. Patients reported a significant decrease in the number of sexual thoughts, sexual satisfactions, and vaginal lubrication after becoming menopausal (McCoy, 1985). In a study of 100 naturally menopausal women, both sexual desire and activity decreased compared with that during the premenopausal period. Women reported loss of libido, dyspareunia, and orgasmic dysfunction, with 86 percent reporting no orgasms after menopause (Tungphaisal, 1991).

Lower Reproductive Tract Changes

Estrogen receptors have been identified in the vulva, vagina, bladder, urethra, pelvic floor musculature, and endopelvic fascia. These structures thus share a similar hormonal responsiveness, including susceptibility to the estrogen deprivation that can develops after menopause, in the postpartum period during lactation, or with hypothalamic amenorrhea.

Without estrogen's trophic influence, the vagina loses collagen, adipose tissue, and ability to retain water (Sarrel, 2000). As vaginal walls shrink, rugae flatten, and the vagina attains a flat-walled, pale-pink appearance. The surface epithelium thins to a few layers of cells, markedly reducing the ratio of superficial to basal cells. As a result, the vaginal surface is left friable and prone to bleeding

with minimal trauma. The blood vessels in the vaginal walls narrow, and over time the vagina itself contracts and loses flexibility. In addition, vaginal pH becomes more alkaline and a pH greater than 4.5 is typically observed with estrogen deficiency (Caillouette, 1997; Roy, 2004). An alkaline pH creates a vaginal environment less hospitable to lactobacilli and more susceptible to infection by urogenital and fecal pathogens. In addition to vaginal changes, as estrogen production wanes in the later menopausal transition, the vulvar epithelium gradually atrophies and secretions from sebaceous glands diminish. The labia minora become paler and smaller. As a result of these changes, the clinical syndromes associated with vulvovaginal atrophy include vaginal dryness and irritation, dyspareunia, and recurrent urinary tract infections (Society of Obstetricians and Gynaecologists of Canada, 2005).

Dyspareunia and Sexual Dysfunction

Complaints of dyspareunia and other forms of sexual dysfunction are extremely common in menopausal patients. Laumann and associates (1999) studied the prevalence of sexual dysfunction in postmenopausal women and found that 25 percent complained of some degree of dyspareunia. They found that painful intercourse correlated with sexual problems, including lack of libido, arousal disorder, and anorgasmia. Although dyspareunia in this population is generally attributed to vaginal dryness and mucosal atrophy secondary to loss of ovarian hormones, prevalence studies suggest a decrement in all aspects of female sexual function are associated with midlife (Dennerstein, 2005).

The reduction in ovarian estrogen results in a decline in vaginal lubrication, atrophic vaginitis, and decreased blood flow and vasocongestion with sexual activity. This leads to genital changes including ischemia, thinning skin, and decline in size of the introitus, labia, vagina, and clitoris (Alexander, 2003). Reduced testosterone levels have been implicated in genital atrophy as well.

Urogenital conditions such as prolapse or incontinence correlate strongly with sexual dysfunction (Barber, 2002; Salonia, 2004). Patients with urinary incontinence are likely to have pelvic-floor hypotonus dysfunction which may cause pain on deep penetration due to lack of pelvic stability. Hypertonic or dyssynergic pelvic-floor muscles, which are commonly seen in patients with urinary frequency, constipation, and vaginismus, are often associated with superficial pain and friction during intercourse (Handa, 2004). The presence of organ prolapse contributes to dyspareunia as does a history of a gynecologic surgical procedure that may cause dyspareunia by shortening the vagina (Goldberg, 2001).

Other medical conditions such as arthritis, hip or lumbar joint pain, or fibromyalgia may contribute to vaginal or pelvic pain with intercourse. Pain may be due to radiation of pain from trigger points in the trunk, buttocks, or pelvic-floor muscles, or from possible pudendal nerve entrapment. Chronic pelvic pain or abdominal and vulvar scars or adhesions may also be contributors to sexual dysfunction (see Chap. 11, Chronic Pelvic Pain).

Urogenital

As was stated earlier, there are estrogen and progesterone receptors in most pelvic floor muscles and ligaments. Due to low estrogen production in late menopause or after oophorectomy, genitourinary atrophy may lead to a variety of symptoms that affect quality of life. Urinary symptoms may include dysuria, urgency, and recurrent urinary tract infections (Notelovitz, 1989).

Specifically, thinning of urethral and bladder mucosa may lead to urethritis with dysuria, urge incontinence, and urinary frequency. In addition, urethral shortening associated with menopausal atrophic changes may result in genuine stress urinary incontinence. For example, Bhatia and colleagues (1989) showed that estrogen therapy may improve or cure stress urinary incontinence in more than 50 percent of treated women, presumably by exerting a direct effect on urethral mucosa coaptation (see Chap. 23, Urethral Coaptation). Accordingly, a trial of hormone therapy should be considered prior to surgical correction of incontinence in women with vaginal atrophy.

Alternatively, some studies have not found an association between incontinence and menopausal status. Sherburn and colleagues (2001) performed a cross-sectional study of Australian women aged 45 to 55 years. In this population, they identified a 15-percent prevalence of incontinence. Associated risk factors included gynecologic surgery, higher BMI, urinary tract infections (UTIs), constipation, and multiparity. Subsequently, these investigators studied a subset of 373 premenopausal females during 7 years to determine if menopausal transition itself was associated with an increased incidence of incontinence. In this group of women, the overall incidence of incontinence was 35 percent, with no increase associated with menopause. Incontinence was most closely related to hysterectomy during the course of the study.

In addition to incontinence, pelvic organ prolapse rates increase with advancing age. Importantly, vaginal relaxation with cystocele, rectocele, and uterine prolapse are not a direct consequence of estrogen deprivation, as many factors play a role in pelvic floor relaxation (Fig. 21-11) (see Chap. 24, Pathophysiology).

FIGURE 21-11

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Prolapse of the anterior vaginal wall. *(Courtesy of Dr. Marlene Corton.)*

PATIENT EVALUATION

Clinical goals of the menopausal transition evaluation are to optimize a woman's health and well-being during and after this transition. This is an excellent time for a detailed health evaluation, including a complete medical history, physical examination, and laboratory studies. Risk factors for such common health problems such as obesity, osteoporosis, heart disease, diabetes mellitus, and certain cancers should be assessed, and then managed (see Chap. 1, Preventive Care). Counseling about diet, exercise, alcohol moderation, and smoking cessation are imperative if applicable.

DIAGNOSIS

The diagnosis of menopausal transition can usually be made with documentation of age-appropriate symptoms and careful physical examination (Table 21-7). Clearly, a 50-year-old woman with menstrual irregularity, hot flushes, and vaginal dryness should be considered to be in menopausal transition. Other testing such as FSH or estradiol levels can be performed to document ovarian failure. However, in the menopausal transition group, FSH levels may be normal. Even when much younger women present with similar symptoms, evaluation should also include FSH measurement. If ovarian failure occurs before 40 years, it is usually pathologic. Thus, investigation for chromosomal abnormalities, infections, autoimmune disorders, galactosemia, cigarette smoking, or iatrogenic causes such as radiation or chemotherapy should be considered (see Chap. 16, Heritable Disorders).

Table 21-7 Differential Diagnosis of Menopausal Symptoms
Hot flushes, vasomotor symptoms
Hyperthyroidism
Pheochromocytoma
Febrile illness
Anxiety and psychological symptoms
Vaginal dryness, dyspareunia
Bacterial vaginosis
Yeast infection
Pelvic pathology
Poor vaginal lubrication
Marital discord
Primary osteoporosis
Osteomalacia
Primary and secondary hyperparathyroidism
Hyperthyroidism or excess thyroid replacement
Excess corticoid therapy
Increased calcium excretion
Abnormal uterine bleeding
Anovulation
Endometrial cancer
Cervical cancer
Endometrial hyperplasia
Endometrial polyps
Uterine leiomyoma
Urogenital atrophy
Hormone treatment

Physical Examination

A thorough general physical examination should be performed during patient visits to document changes associated with aging and menopausal transition.

CONSTITUTIONAL

Height, weight, and BMI are recorded and can be used to counsel women about physical exercise and weight loss or weight gain. Moreover, assessment of weight distribution and waist circumference may identify those with truncal obesity, who carry greater risks for other comorbidity. Height loss may be associated with osteoporosis and spinal compression fractures. Therefore yearly height measurement is warranted. Blood pressure monitoring effectively screens for hypertension, which is common in this population.

COGNITIVE

Cognitive decline is unusual in a woman during menopausal transition, but common complaints of forgetfulness or scattered thinking may be part of the normal aging process. In patients who are concerned about cognitive decline, referral to a neurologist is encouraged.

PSYCHOSOCIAL

Evaluation of psychosocial well-being should be part of transition assessment. Clinicians may inquire directly about depression, anxiety, and sexual functioning, or may choose to administer a simple questionnaire to assess for psychosocial issues (see Chap. 13, Diagnosis of Mood Disorders).

DERMATOLOGIC

Skin changes associated with estrogen deficiency include skin thinning and wrinkling. In addition, various skin lesions are commonly associated with aging and photo-aging. Careful inspection for abnormal nevi or excessive sun exposure may prompt referral to a dermatologist for further skin cancer evaluation.

BREAST

During menopausal transition, estrogen levels fall and glandular breast tissue is gradually replaced by fatty tissue. Breast tissue and axillae are carefully inspected and palpated. Nipple discharge, skin changes, nipple inversion, and masses should be documented and evaluated (see Chap. 12, Evaluation of a Breast Lump).

PELVIC EXAMINATION

Examination of the vulva may demonstrate loss of the connective tissue that results in shrinkage of the labia majora. The labia minora may disappear completely, and there is often a narrowing of the introitus. The vulva should be examined for redness, atrophy, or scarring. In those with pain, scar tissue from a past tear or episiotomy, traumatic delivery, or surgery should be noted. Specific areas of tenderness can often be localized with a methodical evaluation of the vulva. Touch with a cotton-swab may locate and reproduce a patient's pain (see Fig. 4-11).

Vaginal examination will typically reveal a narrow vaginal canal and thin vaginal epithelium. The classic appearance of vaginal atrophy includes loss of rugae and a pale, dry vaginal mucosa. Epithelial tissues are often friable, and submucosal petechial hemorrhages may be seen. Markers of vaginal atrophy include a vaginal pH greater than 5.0 and a change in the vaginal wall's maturation index toward basal cell predominance. Culture of the vagina may reveal pathogenic bacteria not normally found in the vagina.

In addition to a standard gynecologic evaluationâ€”that is, bimanual and speculum examinationâ€—external and internal assessment should focus on pelvic and vaginal muscular tone and strength, as well as mobility and integrity of the fascia and connective tissues. The degree of introital flexibility, mucosal dryness, or atrophy is determined. Integrity of the pelvic organs and possible prolapse of the bladder, uterus, or rectum is evaluated by having the patient perform a Valsalva maneuver and observing for bulging of a cystocele, rectocele, or cervical or vaginal prolapse.

Laboratory Testing

GONADOTROPIN LEVELS

There are biochemical changes present, of which a woman may be unaware, prior to evidence of cycle irregularity. For example, in the early follicular phase of the menstrual cycle in many women older than 35 years, FSH levels may rise without a concurrent luteinizing hormone (LH) elevation. This finding is associated with a poor prognosis for future fertility. Specifically, a day-3 FSH level greater than 10 mIU/mL is used in some in vitro fertilization (IVF) programs to route patients into donor egg programs (see Chap. 20, Correction of Diminished Ovarian Reserve). An FSH level greater than 40 mIU/mL has been used to document ovarian failure associated with the menopause.

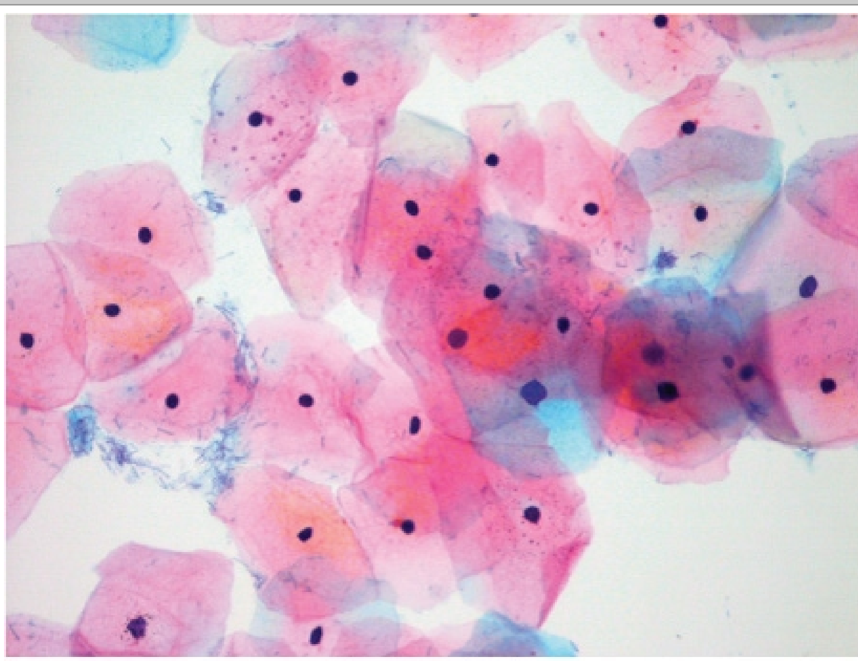
ESTROGEN LEVELS

Estrogen levels may be normal, elevated, or low depending on the stage of menopausal transition. Only at menopause are estrogen levels extremely low or undetectable. Additionally, estrogen levels may be used to assess women's response to hormone treatment. Most clinicians prefer to reach a physiologic serum estradiol range of 50 to 100 pg/mL when selecting and adjusting replacement therapy. Women who receive estradiol pellets as replacement therapy may have elevated serum estradiol values from 300 to 500 pg/mL. These high levels are not uncommon with this replacement method but should be discouraged.

ESTROGEN MATURATION INDEX

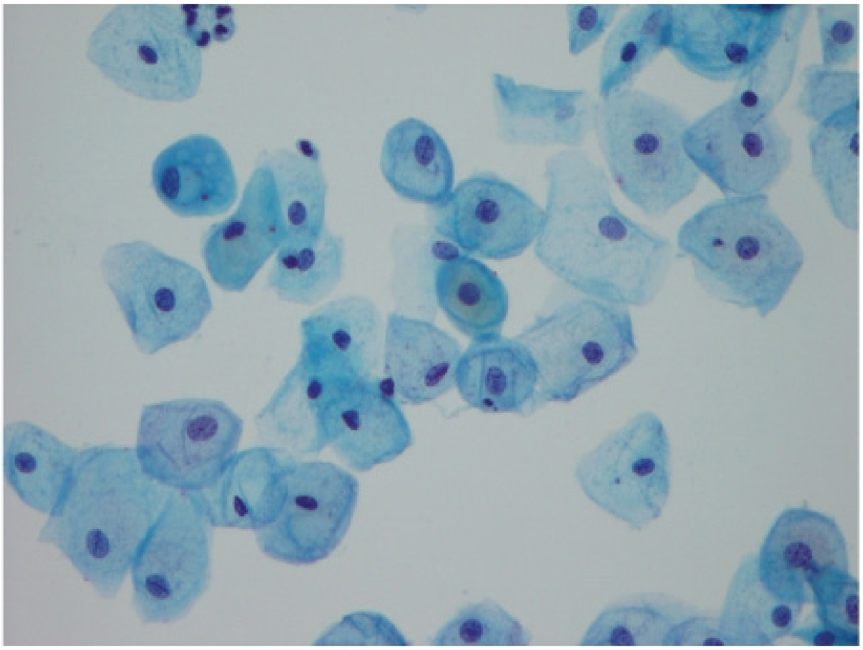
The maturation index (MI) is an inexpensive means to evaluate hormonal influences in women. A specimen to measure the MI may be collected during a vaginal speculum examination at the same time a Pap smear is performed. The index report is read from left to right and refers to the percentage of parabasal, intermediate, and superficial squamous cells appearing on a smear, with the total sum of all three values equaling 100 percent (Fig. 21-12) (Randolph, 2005). For example, an MI of 0:40:60 represents 0 percent parabasal cells, 40 percent intermediate cells, and 60 percent superficial cells. This MI reflects adequate vaginal estrogenization. A shift to the left indicates an increase in parabasal or intermediate cells, which denotes low estrogen levels. Conversely, a shift to the right reflects an increase in the superficial or intermediate cells, which is associated with higher estrogen levels.

FIGURE 21-12



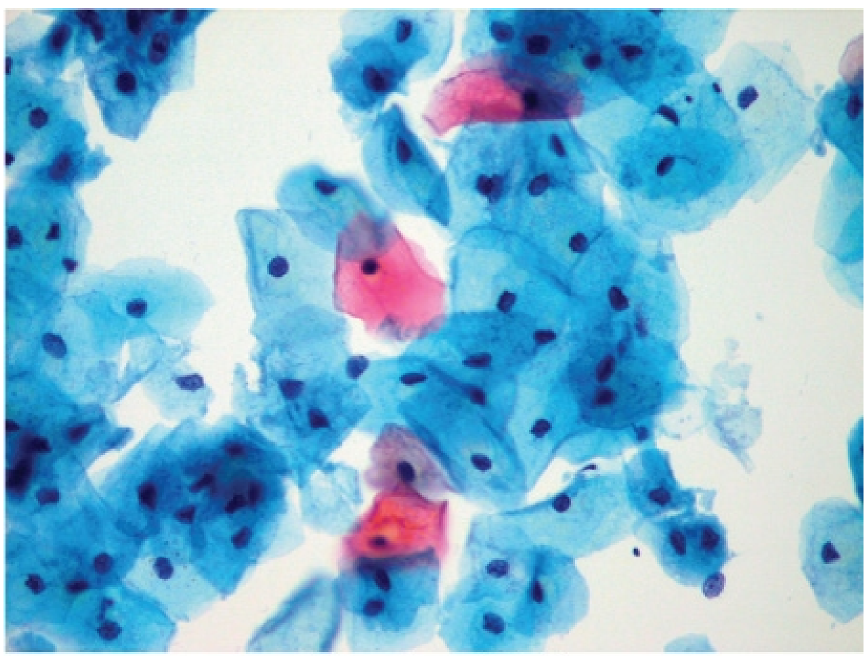
A Estrogenized

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



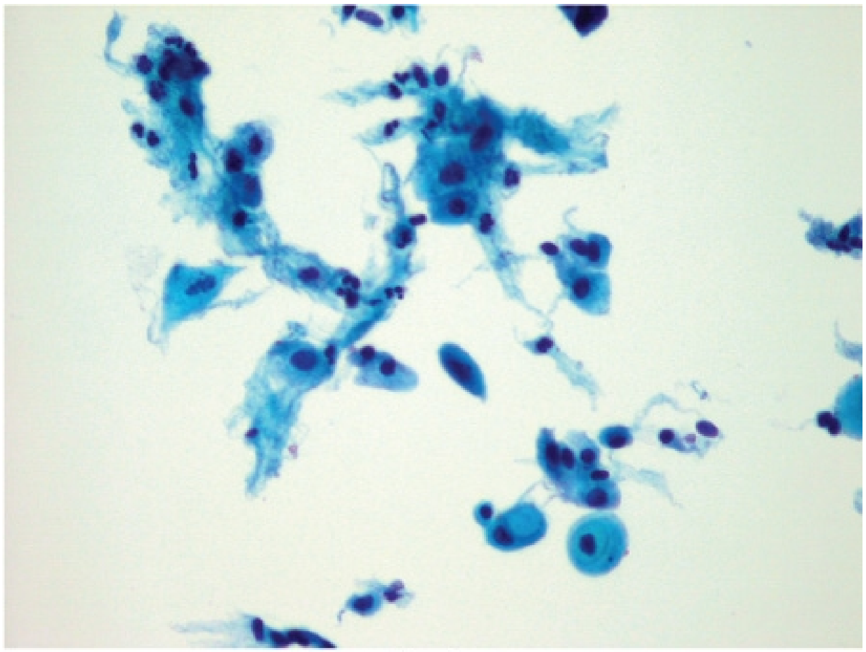
B Reproductive Age

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



C Progesterone Effect

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photomicrographs of cytologic specimens illustrate key points of the maturation index. This index provides insight into the cytohormonal status of the patient and is based on a count of parabasal, intermediate, and superficial (P:I:S) cells. Generally, a predominance of superficial or superficial and intermediate cells (**A** and **B**) is seen in reproductive-aged women. A predominance of intermediate cells (**C**) is seen in the luteal phase, pregnancy, with amenorrea, and in newborns, premenarchal girls, and women in early menopausal transition. A predominance of parabasal cells (**D**) is seen in menopausal patients with atrophy. *(Courtesy of Dr. Raheela Ashfaq).*

An ideal MI vaginal specimen consists of freely exfoliating squamous cells from the upper third of the vaginal wall. Avoiding the cervical area, the vaginal wall secretions are gently scraped with a spatula or saline-moistened swab. Immediately after collection, the specimen is transferred to a microscope slide. Cells are either suspended in a small amount of saline (as in a wet prep) or smeared to the slide and fixed with 95-percent ethanol spray fixative.

URINARY AND SERUM MARKERS OF BONE RESORPTION AND FORMATION

Remodeling is a normal, natural process that maintains skeletal strength, enables repair of microfractures, and allows calcium homeostasis. During remodeling, osteoblasts synthesize a number of cytokines, peptides, and growth factors that are released into the circulation. Their concentration thus reflects the rate of bone formation. Bone formation markers include serum osteocalcin, bone-specific alkaline phosphatase, and procollagen I carboxy terminal propeptide (PICP) (Table 21-8).

Table 21-8 Analytes Considered Markers of Bone Resorption and Formation

Resorption	Formation
Urinary calcium	Bone-specific alkaline phosphatase
Tartrate resistant acid phosphatase	Osteocalcin
Bone sialoprotein	Procollagen I extension propeptides
Cross-links	Carboxy terminal (PICP)
Pyridinoline	Amino terminal (PINP)
Deoxypyridinoline	
N-telopeptide	
C-telopeptide	
C-terminal telopeptide of type I collagen	

PICP = procollagen I propeptide, c-terminal; PINP = procollagen I propeptide, n-terminal.

Osteoclasts produce bone degradation products that are also released into the circulation and are eventually cleared via the kidney. These include collagen cross-linking peptides and pyridinolines, which can be measured in the blood or urine and enable estimation of bone resorption rates. Bone resorption markers include urinary hydroxyproline, urinary pyridinoline (PYR), and urinary deoxypyridinoline (D-PYR), as well as collagen type I cross-linked N telopeptide (NTX) and collagen type I cross-linked C telopeptide (CTX).

Markers of bone formation and resorption are of value in estimating bone-remodeling rates. These biochemical markers may be used to identify fast bone losers. Numerous cross-sectional studies have shown that bone remodeling rates as evaluated by markers increase at menopause and remain elevated. Bone remodeling rates in menopausal women correlate negatively with BMD.

Most prospective studies evaluating the relationship between bone remodeling and rates of bone loss have been short-term and have been limited by the precision error of densitometry. Garnero and colleagues (1994) prospectively evaluated the utility of bone markers to identify fast bone losers in a large cohort of healthy menopausal women over 4 years. They found that higher levels of bone formation and resorption markers were significantly associated with faster and possibly greater BMD loss.

Markers of bone resorption may be useful predictors of fracture risk and bone loss. Elevation of these markers may be associated with an increased fracture risk in elderly women, although data are not uniform. The association of markers of bone resorption with hip fracture risk is independent of BMD, but a low BMD combined with high bone resorption biomarker doubles the risk associated with either of these factors alone. Biomarker measurements are also currently limited by their high variability within individuals. Additional studies with fracture endpoints are needed to confirm the usefulness of these markers in individual patients.

Biomarkers may also be of value in predicting and monitoring response to potent antiresorptive therapy in clinical trials. Normalization of bone formation and resorption marker levels following therapy has been observed in prospective trials. Reduction in biochemical marker levels appears to be correlated with a decrease in vertebral fracture incidence in some studies, but is not necessarily always predictive of response to therapies.

Bone remodeling markers should not yet be used for routine clinical management. Additional studies are needed to confirm their use in individual patients. However, with refinement of assay technology and better understanding of biological variability, it is likely that they will become a useful adjunct for risk assessment and management.

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THE MATURE WOMAN: INTRODUCTION

The typical "mature woman" is aged 40 years or older and has completed childbearing. During their late 40s, most women enter menopausal transition, and this period of physiologic change is usually completed between ages 51 and 56 (see Chap. 21). Menopause marks a defining point in this transition. Specifically, it is defined by the World Health Organization as the point in time of permanent menstruation cessation due to loss of ovarian function. Clinically, the menopause refers to a point in time that follows 1 year after the cessation of menstruation.

After ovarian senescence, declining estrogen levels have specific effects on many tissues. Some effects lead to physical symptoms, such as vasomotor symptoms and vaginal dryness, whereas others are metabolic and structural changes. These include osteopenia, osteoporosis, skin thinning, fatty replacement of the breast, and genitourinary atrophy. As a result, postmenopausal women have specific issues associated with aging and estrogen loss that may negatively affect their individual health.

For many years menopause was seen as a "deficiency disease" much like hypothyroidism. For this reason, hormone replacement therapy has been used in one form or another for more than 100 years. The history and controversies surrounding this treatment are discussed in detail, as are current recommendations for the treatment of menopausal symptoms.

HORMONE TREATMENT: HISTORY AND CONTROVERSIES

In the recent past, hormone treatment (HT) was prescribed, in good faith, to women for many potential health benefits, based on available observational studies of the time. It was thought that HT, in addition to its beneficial role in prevention and treatment of osteoporosis, could protect against cardiovascular disease, stroke, and dementia. However, recent prospective, randomized, and blinded studies have challenged the validity of earlier observational studies. Thus, clinicians should understand the history and controversies surrounding HT to accurately counsel their patients on the complexities and appropriate use of HT.

Early Estrogen Administration Trends

Estrogen treatment (ET) for menopausal symptom relief gained popularity in the 1960s and 1970s. Author and gynecologist Robert Wilson's book *Feminine Forever* was published in 1968. In it, he wrote that "Women who use the drug (estrogen) will be much more pleasant to live with and will not become dull and unattractive" (Bell, 1990). Wilson was a prolific lecturer. His book was widely read and was influential, in part, for some of the enthusiasm for ET and its "preservation of youth" and prevention of chronic disease.

By the mid-1970s, more than 30 million prescriptions were written for estrogen each year, and half of all menopausal women were using HT for a median of 5 years. Premarin (conjugated equine estrogen, Wyeth Pharmaceuticals, Philadelphia, PA) was the fifth most prescribed drug in the marketplace.

In 1975, a study revealed a connection between endometrial cancer and estrogen replacement. Investigators found a 4.5-times greater risk of this cancer in those using estrogen (Smith, 1975). As a result, the U.S. Food and Drug Administration (FDA) ordered labeling changes to state this higher risk.

Estrogen as a Prevention Tool

In the 1980s, progestins were added to therapy regimens to significantly reduce endometrial cancer risks. During that same time, estrogens were documented by several studies to prevent bone loss (Gambrell, 1983). A number of observational studies also suggested that estrogens prevented development of coronary heart disease and other conditions, such as Alzheimer disease.

However, in 1985, conflicting reports from the Framingham Heart Study and the Nurses' Health Study were published.

The Framingham Heart Study, an observational study of 1,234 women, showed that those who took hormones had a 50-percent elevated risk of cardiac morbidity and more than a twofold risk for cerebrovascular disease (Wilson, 1985). In the same edition of the *New England Journal of Medicine,* the much larger Nurses' Health Study, with 121,964 women, found significantly lower rates of heart disease in postmenopausal women taking estrogen compared with postmenopausal women not taking estrogen (Stampfer, 1985). Numerous subsequent articles published in medical periodicals reported on the protective effects that combination HT provided menopausal women against cardiovascular disease and osteoporosis.

Current thinking is that that these early nonrandomized, unblinded, observational studies included samples of women who were not necessarily representative of the entire population of postmenopausal women. These hormone users tended to have superior health care access and to be thinner, wealthier, and healthier overall (Grodstein, 2003; Prentice, 2006). An additional source of confounding and possible selection bias is suggested to be the timing of initiation of hormone therapy in relation to the underlying state of the vasculature. Some investigators have hypothesized that estrogen may delay the onset of the earliest stages of atherosclerosis, which are more likely to be present in younger women, but it may be ineffective or even trigger events in the presence of existing advanced lesions such as those found in older women (Mendelsohn, 2005). The potential existence of a window of opportunity to reduce cardiovascular disease is supported by animal and laboratory studies (Grodstein, 2003). The impacts of these characteristics, biases, and timing in initiation may have led, in part, to favorable outcomes attributed to estrogen in observational trials.

The Postmenopausal Estrogen/Progestin Interventions Trial

Because of data available in the late 1980s, estrogens were prescribed, not only for vasomotor symptom relief, but also for prevention of other conditions. In 1995, the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial results were published and suggested benefit for coronary heart disease risk. In this study, menopausal women with a mean age of 56 years were randomly allocated to one of five treatments: (1) placebo, (2) estrogen alone, (3) estrogen plus cyclic medroxyprogesterone acetate (MPA), (4) estrogen plus cyclic micronized progesterone, or (5) estrogen plus continuous MPA (The Writing Group for the PEPI Trial, 1995). Primary outcomes studied in the 875 women evaluated during 3 years included assessment of systolic blood pressure and measurement of serum lipid, insulin, and fibrinogen levels. The PEPI trial documented that low-density lipoprotein cholesterol levels were decreased similarly in all groups administered estrogen compared with placebo. In addition, high-density lipoprotein levels were increased in the four treatment groups receiving estrogen. Levels were most substantially increased in women solely given estrogen. An intermediate effect was noted in those prescribed conjugated equine estrogen (CEE) and micronized progesterone, whereas the smallest increase followed CEE and MPA administration. Fibrinogen was increased in the placebo group compared with groups given hormones. However, no differences were identified among any treatment groups in systolic blood pressure or glucose-challenged insulin levels. Clinical outcomes were also reported, and complications were few. Of these, all occurred in the HT-treated groups and included one cardiac arrest, two myocardial infarctions, and two cerebrovascular events (American College of Obstetricians and Gynecologists, 2004).

Heart and Estrogen/Progestin Replacement Study

With results published in 1998, the Heart and Estrogen/Progestin Replacement Study (HERS) described cardiac morbidity in 2,763 women with pre-existing heart disease (Hulley, 1998). These women received estrogen as secondary prevention for further cardiac disease progression. First-year findings showed an increase in myocardial infarctions (MIs) in women who received CEE with continuous MPA. However, after an average treatment duration of 4 years, there was no difference in risks of cardiovascular death or nonfatal MI between treatment groups, with a hazard ratio of 0.99 (95 percent CI 0.81 to 1.22).

The HERS trial represented the first randomized clinical trial at variance with previous observational data and created significant confusion for both clinicians and their patients. There was still widespread belief that hormones prevented heart disease, but the HERS data caused many clinicians and scientists to begin to seriously question the cardioprotective effects of hormones. In June 2002, the HERS II results were published by Grady and colleagues (2002) and also showed that HT was not beneficial in the secondary prevention of heart disease even after 6.8 years. A subsequent re-analysis of the Nurse's Health Study focusing on early hazard among women initiating HT during the monitoring period showed a similar time trend, with early harm, as did the HERS

trial (Grodstein, 2001).

Women's Health Initiative

After an unsuccessful effort in 1990 to obtain FDA approval for HT as a preventive treatment for coronary heart disease, the need for randomized clinical trials to demonstrate conclusive benefit was widely acknowledged. As a result, before the results from the PEPI trial and HERS trials, the National Institutes of Health (NIH) launched the Women's Health Initiative (WHI) in 1993. This was a major study to evaluate the putative beneficial and protective effects of HT on common chronic diseases of aging. The WHI examined the effect of a combined CEE and MPA drug compared with placebo in 16,608 healthy postmenopausal women aged 50 to 79 years (mean of 63.3 years) who had not had a hysterectomy (Rossouw, 2002). Specific end points were evaluated: coronary heart disease, venous thrombotic events, breast cancer, colon cancer, and bone fractures. Concurrently, the study also compared CEE with placebo in postmenopausal women without a uterus (the estrogen-only arm).

As part of the original WHI study design, investigators predetermined targets for CHD (anticipated benefit) and breast cancer (anticipated risk) as primary disease end points. This design dictated that if the incidence of an end point was exceeded within a given period, the study would be terminated. Moreover, combined end points were weighted into a "global index", which if exceeded within a given time period, would result in study termination. After a mean 5.2 years of monitoring, the estrogen and progestin arm of WHI was halted early upon recommendation of its Data and Safety Monitoring board because overall risks exceeded the benefits. In July 2002, results were released to the media. This preceded journal publication of the data and timely education of health care providers. Chaos ensued while physicians and patients evaluated research facts and before recommendations could be made.

In a subsequent detailed analysis of cardiovascular end points, the hazard for cardiovascular death or nonfatal MI was 1.24 (95 percent CI 1.00 to 154). This translated into 188 actual cases in the hormone group and 147 in the placebo group (Anderson, 2004). However, there were no significant differences in coronary revascularization, hospitalization for angina, confirmed angina, acute coronary syndrome, or congestive heart failure.

To explore the issue of timing of initiation of hormone therapy and the influence on cardiovascular disease, Rossouw and colleagues (2007) did a secondary analysis of the WHI. They looked specifically at the effect of HT on coronary heart disease (CHD) and stroke across categories of age and years since menopause in the combined trial. They found that women who initiated hormone therapy closer to menopause tended to have reduced CHD risk compared with the increase in CHD risk among women more distant from menopause. They found that for women with less than 10 years since menopause began, the hazard ratio for CHD was 0.76; with 10 to 20 years since menopause, 1.10; and with 20 or more years, 1.28.

In evaluating data by age, lower risk was found for young women and higher risk for older patients. Specifically, for the age group of 50 to 59 years, the hazard ratio (HR) for CHD was 0.93 or two *fewer* events per 10,000 person years; for the age group 60 to 69 years, 0.98 or 1 *fewer* event per 10,000 person years; and for those 70 to 79 years, 1.26 or 19 *extra* events per 10,000 person years. Hormone therapy increased the risk of stroke (HR 1.32; 95% CI, 1.12 to 1.56) and risk did not vary significantly by age or time since menopause. Rossouw and colleagues concluded that women who initiated hormone therapy closer to menopause tended to have reduced CHD risk compared with the increase in CHD risk among women more distant from menopause.

Concurrent with the WHI, a similarly constructed study, the Women's International Study of Long Duration Oestrogen after Menopause (WISDOM) began enrollment in 1999. This trial was stopped following halting of the WHI. Analyzing data collected from this study, Vickers and colleagues (2007) found hormone replacement therapy increases cardiovascular and thromboembolic risk when started many years after the menopause. These finding echoed those of the women's health initiative study.

CURRENT APPROACH TO HORMONE REPLACEMENT ADMINISTRATION

Summary of Risks and Benefits

As a result of these and other studies, clinicians now know more about the risks and benefits of HT than ever before. In the many reviews and discussions following WHI, most clinicians agree that HT is associated with an increased risk of CHD in older menopausal women, and an increased risk of breast cancer, stroke, venous thromboembolism, and cholecystitis. Breast cancer appears only to be a risk factor with long-term use (>5 years). Two studies have shown an increase in ovarian cancer risk with

long-term use (>10 years), but not with short-term use (<5 years) (Danforth, 2007; Lacey, 2006). However, other studies have not confirmed this risk (Noller, 2002).

In contrast, several long-term benefits are noted with HT. These include increased bone mineral density and decreased rates of fracture and colorectal cancer. In addition to its individual benefits, HT's effects on mortality rates have been examined. A meta-analysis done by Salpeter and associates (2004) pooled data from 30 randomized trials from 1966 through April 2003. Calculations from 26,708 participants revealed that the total mortality rate associated with HT was 0.98 (95 percent confidence). Of note, HT reduced mortality in women younger than 60 years (odds ratio 0.61) but not in women older than 60 (odds ratio 1.03). These investigators suggest that once coronary heart disease is established, HT has no effect in reversing disease progression. Moreover, the incidence of cardiovascular events can potentially increase in older groups due to an increased risk for blood clots. Similarly, Rossouw's group (2007) showed a nonsignificant tendency for the effects of hormone therapy on total mortality to be more favorable in younger than older women.

Summary of Current Use Indications

Based on current literature, HT is indicated today only for treatment of vasomotor symptoms and vaginal atrophy and for osteoporosis prevention or treatment. The current standard of care dictates re-evaluation of the need for therapy at 6- to 12-month intervals. Hormone therapy should be prescribed in the lowest effective dose for the shortest period of time. Accordingly, bone-specific agents would likely be more appropriate in women requiring long-term osteoporosis prevention or treatment.

For women with a uterus, a progestin should be combined with an estrogen to lower risks of endometrial cancer. Progestins may be prescribed daily with estrogen, and this dosing is termed *continuous therapy* . Amenorrhea typically results from this regimen. Alternatively, estrogen may be administered for 25 days each month and a progestin added for the final 10 days. Drugs are withdrawn for 5 days and endometrial sloughing and bleeding follows. This *cyclic therapy* is most commonly used in those during menopausal transition, whereas continuous therapy is usually selected for women following menopause.

Oral progestins are most commonly prescribed, although a progestin-containing intrauterine device (Mirena, Berlex, Wayne, NJ) provides another option (see Chap. 5, Levonorgestrel-Containing Intrauterine Device). In addition, combined estrogen and progestin products are available for either oral or transdermal use. Low-dose combination oral contraceptives are effective in the young perimenopausal woman and have the additional benefit of pregnancy prevention.

Importantly, estrogen is contraindicated in women who exhibit one or more of the following: known or suspected breast carcinoma, known or suspected estrogen-dependent neoplasia, abnormal genital bleeding of unknown etiology, known or suspected pregnancy, and those with active liver disease (Table 22-1). In addition, data show a twofold increase in the risk of venous thromboembolic events (VTEs) in users of HT. Estrogens, particularly those given orally, stimulate hepatic production of clotting factors. Accordingly, HT is also contraindicated in women with a prior history of VTEs.

Table 22-1 Warnings and Precautions with Estrogen Administration
Estrogen should not be used in women with any of the following conditions: 1. Undiagnosed abnormal genital bleeding 2. Known, suspected, or history of breast cancer 3. Known or suspected estrogen-dependent neoplasia 4. Active deep vein thrombosis, pulmonary embolism, or history of these conditions 5. Active or recent (e.g., within the past year) arterial thromboembolic disease (e.g., stroke or myocardial infarction) 6. Liver dysfunction or disease 7. Known hypersensitivity to the ingredients of the estrogen preparation 8. Known or suspected pregnancy. There is no indication for estrogen in pregnancy. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins from oral contraceptives inadvertently during early pregnancy
Estrogen should be used with caution in women with the following conditions: 1. Dementia 2. Gallbladder disease 3. Hypertriglyceridemia 4. Prior cholestatic jaundice 5. Hypothyroidism 6. Fluid retention plus cardiac or renal dysfunction 7. Severe hypocalcemia 8. Prior endometriosis 9. Hepatic hemangiomas

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Ultimately, the decision regarding whether or not to begin HT is a personal one, to be decided by the patient with guidance from her health care provider.

SYMPTOMS OF MENOPAUSE

Common early symptoms of menopause include vasomotor symptoms, insomnia, irritability, and mood disorders, which can be caused by vasomotor instability. Physical changes include vaginal atrophy, urinary stress incontinence, and skin atrophy. Long-term health risks that have been attributed to the hormonal changes from menopause include osteoporosis, cardiovascular disease, and in some studies, Alzheimer disease, macular degeneration, and stroke.

Treatment of Vasomotor Symptoms

The most frequent symptom of the menopausal transition is vasomotor symptoms, also known as hot flushes or hot flashes (see Chap. 21, Incidence). Following menopause, hot flushes are still pervasive and are experienced by 50 to 85 percent of postmenopausal women. Significant distress results for approximately 25 percent of women. Sleep disturbances can lead to lethargy and depressed mood.

The frequency of hot flushes does decrease with time. In the PEPI trial, the percentage of women taking placebo who experienced vasomotor symptoms declined from 56 percent at their entry into the study to 30 percent by their third year in the trial (Greendale,

1998). Only a small percentage of women continue to suffer from hot flushes 10 years after their menopause. Fifteen years after menopause, approximately 3 percent of women report frequent hot flushes, and 12 percent report moderate to severe vasomotor symptoms (Barnabei, 2002; Hays, 2003).

HORMONAL THERAPY ESTROGEN

Therapy Effectiveness

Hormonal therapy is the most effective treatment for hot flushes and sleep disturbances, thereby improving quality of life in symptomatic women. The value of such treatment has been demonstrated in numerous randomized controlled trials (RCTs) (Nelson, 2004). Maclennan and associates (2004) performed a systematic review of 24 RCTs involving 3,329 women who had moderate to severe hot flushes. These investigators found that HT reduced the frequency of hot flushes by approximately 18 events per week, that is, approximately 75 percent compared with placebo. The severity of vasomotor symptoms also was reduced significantly. Moreover, in the PEPI trial, all treatment arms were more effective than placebo in reducing vasomotor symptoms. There were no significant differences between specific hormone regimens (Greendale, 1998).

Estrogens Approved for Vasomotor Symptoms

Estrogen can be administered by oral, parenteral, topical, or transdermal routes with similar effects (Table 22-2). Within these groups, several different formulation choices are available. Continuous estrogen therapy is recommended, although doses and route of administration can be changed relative to patient preference. In the United States, oral estrogens are the most popular. Transdermal estrogen patches avoid the liver's first pass effect and offer the convenience of less frequent administration (once or twice weekly). The lowest effective dose and duration of therapy are unknown, but this "mantra" is cited by most major menopause organizations for ensuring safety. For treatment of vasomotor symptoms, the FDA has approved all oral estrogen formulations, most transdermal patch formulations, a topical gel, and one intravaginal estrogen product. However, the low-dose estrogen patch, Menostar, (Berlex, Wayne, NJ) has not been approved for this indication.

Table 22-2 Selected Estrogen and Progestin Preparations for the Treatment of Menopausal Vasomotor Symptoms

Preparation	Generic Name	Brand Name	Doses (mg)
Estrogen[a]			
Oral	Conjugated estrogens	Premarin	0.3, 0.45, 0.625, 0.9, 1.25
	17β-estradiol	Estrace	0.5, 1.0, 2.0
Transdermal	17β-estradiol	Alora	0.025, 0.05, 0.075, 0.1 (patch applied twice weekly)
		Climara	0.025, 0.0375, 0.05, 0.075, 0.1 (patch applied weekly)
Vaginal	Estradiol acetate	Femring vaginal ring[d]	0.05, 0.1 (inserted every 90 days)
Progestogen			
Oral	MPA	Provera	2.5, 5.0, 10.0
	Micronized progesterone	Prometrium	100, 200 (in peanut oil)
Vaginal	Progesterone	Prochieve 4%	45

Combination preparations			
Oral sequential[b]	Conjugated estrogens and MPA	Premphase	0.625 conjugated estrogens plus 5.0 MPA
Oral continuous[c]	Conjugated estrogens and MPA	Prempro	0.625 conjugated estrogens plus 2.5 or 5.0 MPA; 0.45 conjugated estrogens plus 2.5 MPA; or 0.3 or 0.45 conjugated estrogens plus 1.5 MPA
Transdermal continuous[c]	17β-estradiol, norethindrone acetate	Activella	1.0 estradiol plus 0.5 norethindrone
	17β-estradiol, levonorgestrel	Climara Pro	0.045 estradiol plus 0.015 levonorgestrel (patch applied weekly)
	17β-estradiol, norethindrone acetate	CombiPatch	0.05 estradiol plus 0.14 or 0.25 norethindrone (patch applied twice weekly)

MPA = medroxyprogesterone acetate.

[a] Hormone therapy can cause uterine bleeding, breast tenderness, and headache. Doses of estrogen that are approxi-mately biologically equivalent include the following: 0.625 mg of Premarin, 1.0 mg of Estrace, and 0.05 mg of Alora, Climara, or Femring.

[b] The first 14 pills contain estrogen and the subsequent pills (15 through 28) contain estrogen with progestin.

[c] Each pill or patch contains estrogen and progestin.

[d] Femring delivers a higher systemic level of estrogen and should be opposed by a progestin in women with a uterus.

From Grady, 2006, with permission.

Progestins

These alone are somewhat effective for treatment of hot flushes in women for whom estrogen is contraindicated, such as those with history of venous thromboembolism or breast cancer. However, adverse effects that include vaginal bleeding and weight gain may limit their use (see Table 22-2).

Beyond mild reduction in hot flushes, progestins used as agents in combined HT offer only one additional benefitâ€”they provide essential protection against estrogen-induced endometrial hyperplasia and cancer in women with a uterus. Clinical trials have shown that progestins provide no meaningful increase in estrogen's benefits to bone. In addition, progestins may attenuate estrogen's beneficial effects on lipids and blood flow.

"Bioidentical" Hormones

Some women, reacting to the media coverage of the WHI, have come to believe that conventional pharmaceutical estrogens hold a clear and present danger. Ironically, more is known about the absolute risks and benefits of HT than almost any other class of drugs on the market.

Although prescriptions for estrogen and progesterone have declined, the use of "bioidentical" hormones has increased significantly. The lay press and self-help hormone books are replete with information suggesting that bioidentical hormones offer the relief that women need with fewer attendant risks. However, current evidence does not support the safety claims reported in much of the advertising for these products. Specifically, the FDA pronounced: "Other doses of CEE and MPA, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials, and in the absence of comparable data, these risks should be assumed to be similar". Thus, these hormones cannot be assumed to be safer than conventional pharmaceutical estrogen or progestins.

CENTRAL NERVOUS SYSTEM AGENTS FOR VASOMOTOR SYMPTOMS

No nonhormonal treatments are currently FDA-approved for management of hot flushes, and long-term studies are not available. However, multiple agents and treatments have been used, and data from short-term trials have been published (Table 22-3). These products provide options for women who decline HT or for those in whom estrogen is contraindicated. However, for many, the side effects or ineffectiveness of these agents compared with HT limits their routine use for this indication.

Table 22-3 Nonhormonal Agents Used as Therapy for Vasomotor Symptoms

Prescription (brand name)	Nonprescription
SSRIs (see Table 13-14)	Black cohosh
Venlafaxine (Effexor)	Dong quai
Fluoxetine (Prozac, Sarafem)	Red clover isoflavones
Paroxetine (Paxil)	Soy isoflavones
Clonidine (Catapres)	Vitamin E
Gabapentin (Neurontin)	
Mirtazapine (Remeron)	
Trazodone (Desyrel)	

SSRI = selective serotonin reuptake inhibitor.

Selective Serotonin Reuptake Inhibitors

Three randomized placebo-controlled trials with the antidepressants venlafaxine (Effexor, Wyeth Pharmaceuticals), fluoxetine (Prozac, Eli Lilly, Indianapolis, IN, and Sarafem, Warner Chilcott, Rockaway, NJ), and paroxetine (Paxil, GlaxoSmithKline, Philadelphia, PA) found modest improvement in hot flushes compared with placebo. Specifically, in a randomized, double-blind, placebo-controlled study, Loprinzi and associates (2000) found that venlafaxine XR decreased hot flush scores by 37 percent with a dosage of 37.5 mg/d, 61 percent with 75 mg/d, and 61 percent with 150 mg/d. Women treated with placebo noted a 27-percent reduction in hot flushes. In 2002, Loprinzi and colleagues studied the effects of fluoxetine, 20 mg/d, on hot flushes. They reported that women treated with the selective serotonin reuptake inhibitor (SSRI) noted only 1.5 fewer vasomotor events compared with those receiving placebo. Finally, in a 6-week trial, Stearns and co-workers (2003) evaluated paroxetine CR, 12.5 mg/d and 25 mg/d dosages, compared with placebo. At both dosages, paroxetine led to approximately three hot flushes per day compared with 1.8 hot flushes per day with placebo. Importantly, benefits of SSRIs should be balanced against drug side effects, which can include nausea, diarrhea, headache, insomnia, jitteriness, fatigue, and sexual dysfunction.

Clonidine

The centrally active α_2 -adrenergic receptor agonist clonidine (Catapres and others), has also been shown to be effective in some clinical trials. Nagamani and colleagues (1987) evaluated clonidine 0.1 mg/d transdermally in an 8-week trial. They reported that 12 of 15 women noted a decrease in vasomotor symptoms compared with 5 of 14 receiving placebo. However, hypotension, dry mouth, dizziness, constipation, and sedation have limited its use. For many women, low-dose clonidine is ineffective, and thus adequate therapy may require substantially higher doses that may magnify side effects.

Gabapentin

Gabapentin (Neurontin, Pfizer, New York, NY) is structurally related to the neurotransmitter γ-aminobutyric acid (GABA), but its exact mechanism of action is unknown. Currently, gabapentin is FDA-approved to treat seizures and neuropathic pain. However, it has extensive off-label use for various other neurologic conditions.

In 2003, Guttuso and associates evaluated the use of gabapentin, 900 mg daily, for treatment of vasomotor symptoms. They found a 45-percent reduction in hot flush frequency compared with a 29-percent reduction with placebo. Adverse effects included dizziness and somnolence. Moreover, Reddy and co-workers (2006) conducted a randomized, double-blinded, placebo-controlled trial in which 60 postmenopausal women received gabapentin, 2400 mg/d; oral conjugated estrogen, 0.625 mg/d; or placebo for 12 weeks. The reductions in the hot flush composite scores for both estrogen (72 percent) and gabapentin (71 percent) were greater than that associated with placebo (54 percent). Headache, dizziness, and disorientation occurred, however, in almost 25 percent of the women treated with gabapentin.

Alpha-Methyldopa

At doses of 500 to 1000 mg/d methyldopa, an antihypertensive, has been shown to be twice as effective as placebo for the treatment of vasomotor symptoms. However, in studies evaluating its efficacy, side effects included dizziness, nausea, fatigue, and dry mouth (Fugate, 2004). Because of significant side effects with this drug and modest improvement in vasomotor symptoms, this drug is not recommended for this indication by the North American Menopause Society (2004).

Bellergal

Bellergal (Bellergal-S, no longer available in the U.S.) is a combined-preparation sedative that contains phenobarbital, ergotamine tartrate, and belladonna alkaloids (Loprinzi, 2005). In randomized double-blind studies, this agent showed either modest or no reduction in vasomotor symptoms compared with placebo. Moreover, in these studies, more than 30 percent of participants withdrew due to treatment ineffectiveness or side effects. Adverse reactions included dry mouth, dizziness, skin rash and drowsiness. Moreover, barbiturates are addictive and should not be recommended for long-term use. Because of its limited efficacy and significant side effects, this agent is not recommended for this indication (North American Menopause Society, 2004).

COMPLEMENTARY AND ALTERNATIVE MEDICINE

In 2005, out-of-pocket expenditures for alternative therapies were estimated at nearly $30 billion dollars, which was more than the out-of pocket expenditures for all physician services that year. By 2000, 34 percent of adults in the United States used complementary and alternative medicine (CAM). In 2002, 49 percent of women in the U.S. and Canada used CAM, and the trend seems to be increasing (Newton, 2002).

Phytoestrogens

Phytoestrogens (isoflavones) are plant-derived compounds that bind to estrogen receptors and have both estrogen agonist and antagonist properties. They are found in soy products and red clover. Small studies evaluating their effectiveness for the treatment of vasomotor symptoms have noted no efficacy or mixed results (Krebs, 2004).

Soy Products

Although the mechanisms of action of soy and dietary isoflavones are not fully understood, they appear to involve binding to the estrogen receptor. For this reason, one should not assume these dietary supplements are safe for women with estrogen-dependent cancers.

For treatment of hot flashes, data supporting isoflavone efficacy are mixed. Albertazzi and colleagues (1998) provided a pure dietary soy supplement that contained 40 mg of protein and 76 mg of isoflavones. In women using this supplement, a 45-percent reduction in vasomotor symptoms was noted compared with a 30-percent reduction in women receiving placebo. Cheng and associates (2007) provided 60 mg of isoflavones or placebo for 3 months to symptomatic women. They noted that isoflavone treatment reduced hot flashes by 57-percent. In contrast, in a double-blind clinical trial with breast cancer survivors, Quella and colleagues (2000) found no difference in vasomotor symptoms between women given soy tablets containing 150 mg of isoflavones per day and those administered placebo.

The effects of soy protein found in various food preparations are not bioequivalent. Even soy foods are not necessarily reliable sources of biologically active isoflavones. For example, the alcohol processing often used in the manufacture of tofu and soymilk removes the biologically active forms, the aglyconic isoflavones. Accordingly, soy food producers have recognized public interested in isoflavone supplements, and many indicate in their product labeling the amounts and forms of isoflavones found in the foodstuff.

Flaxseed

Flaxseed or flaxseed oil (*Linum usitatissimum*) is rich in α-linolenic acid, a form of omega-3 fatty acid. Also known as linseed, flaxseed is touted to reduce inflammation, bone turnover, heart disease, cancer, diabetes, and cholesterol levels. For perimenopausal women, it also is purported to protect against breast cancer, hot flushes, and mood disturbances. However, data regarding flaxseed efficacy for treatment of hot flushes are limited. Lewis and co-workers (2006) conducted a double-blinded, randomized controlled trial in which 87 women were assigned to one of three groups that daily ingested muffins that contained soy, flaxseed, or wheat. This study fund no significant difference in vasomotor symptoms among the three groups. In contrast, Lemay and associates (2002) found 40 g of flaxseed as effective as 0.625 mg of CEE for the treatment of mild menopausal symptoms in a randomized cross-over study comparing the two.

Red Clover

Trifolium pratense is a member of the legume family. It contains at least four estrogenic isoflavones, and is therefore marketed as a source of phytoestrogens. Several studies, however, have failed to demonstrate an effect over placebo in the treatment of menopausal symptoms (American College of Obstetricians and Gynecologists, 2004; Nelson, 2004). For example, a randomized controlled trial of 252 women studied hot flush frequency in women given red clover isoflavone extracts and placebo over 12 weeks. No significant change in hot flush frequency was reported between groups receiving isoflavones and those given placebo (Tice, 2003).

Dong Quai

Also translated as don kwai, dang gui, and tang kuei, this Chinese herbal medicine is derived from the root of *Angelica sinensis* , and is the most commonly prescribed Chinese herbal medicine for "female problems". Within traditional Chinese medicine (TCM) practice, dong quai is suggested to regulate and balance the menstrual cycle, strengthen the uterus, and enrich the blood. It is also said to exert estrogenic activity. Most herbal practitioners seem to agree it is contraindicated during pregnancy and lactation.

In 1997, Hirata and colleagues at Kaiser Permanente conducted a double-blinded controlled clinical trial using a daily dong quai dose of 4.5 g. Women using dong quai and those using placebo *both* reported a 25-percent reduction in hot flushes. Critics of the study have noted that the dose of dong quai was lower than that often used in TCM, and that dong quai is never employed as an isolated intervention. However, its benefit cannot be substantiated based on available evidence.

Dong quai is potentially toxic. It contains numerous coumarin-like derivatives and may cause excessive bleeding or interactions with other anticoagulants. This herbal agent also contains psoralens and is potentially photosensitizing, which increases concerns of sun exposureâ€“related skin cancers.

Black Cohosh

The root of the herb *Cimifuga racemosa* is also thought to have estrogenic properties, although the mechanism of action is unknown. In a randomized placebo-controlled trial in 85 women, it did not decrease the frequency of vasomotor symptoms compared with placebo (Krebs, 2004). Although few adverse effects have been reported, the long-term safety of these products is unknown. Two large NIH-sponsored studies with red clover and black cohosh are ongoing (www.clinicaltrials.gov .).

PHYTOPROGESTINS

Extracts, tablets, and creams derived from yams are claimed to be progesterone substitutes and are frequently touted as a natural source of dehydroepiandrosterone (DHEA). Sterol structures from the plant are used as precursors in the biosynthesis of progesterone, DHEA, and other steroids, but do not have inherent biological activity. Specifically, claims are made that the plant sterol *dioscorea* is converted into progesterone in the body and alleviates "estrogen dominance". Yam extracts are also purported to be effective for uterine cramps. However, there is no human biochemical pathway for bioconversion of dioscorea to progesterone or DHEA in vivo.

In contrast, Mexican yam extract is estrogenic, containing considerable *diosgenin* , an estrogen-like substance found in plants. Some estrogen effects might be expected from eating these yam species, but only if large quantities of raw yams are consumed. Yams from the grocery store generally are not the varieties known to contain significant amounts of dioscorea or diosgenin.

Based on the lack of bioavailability, the hormones in wild and Mexican yam would not be expected to have efficacy. Wild yam extracts are neither estrogenic nor progestational, and although many yam extract products contain no yam, some are laced with progesterone or medroxyprogesterone. Oral ingestion does not produce serum levels. There are no published reports demonstrating the effectiveness of wild yam cream for postmenopausal symptoms.

Vitamin E

In 125 women with a history of breast cancer, vitamin E produced a 25-percent reduction in hot flushes compared with a 22-percent reduction with placebo, a decrease of one hot flush per person per day (Barton, 1998).

ENVIRONMENTAL AND LIFESTYLE CHANGES

Practices that lower core body temperature such as using a fan, dressing in layers, and taking cool showers may temporarily help with night sweats and flushing. Relaxation techniques such as paced respiration can decrease symptoms. Meditation, smoking cessation, and weight loss may also be helpful, as are ingestion of cold foods and beverages.

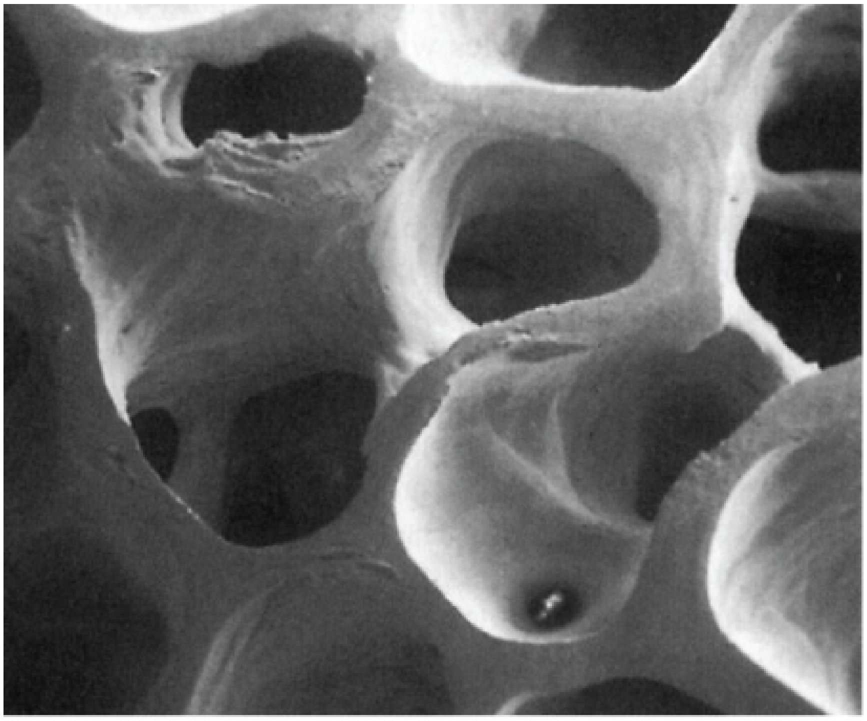
Therapies based on the interaction and the relaxation of the mind and the body for the treatment of menopausal symptoms have been shown to reduce the frequency of hot flushes. Irvin and co-workers (1996) randomized symptomatic menopausal women to relaxation, reading, or control groups. The relaxation group had significant reductions in hot flush intensity, tension, anxiety, and depression compared with the control group, which had no significant changes. Freedman and Woodward (1992) evaluated women with frequent hot flushes who were randomized to paced respiration, muscle relaxation, and placebo biofeedback. In the paced respiration group, there was a significant reduction in the hot flush frequency, although muscle relaxation and biofeedback showed no improvement. The proposed mechanism of action is decreased central sympathetic tone.

Treatment of Osteoporosis

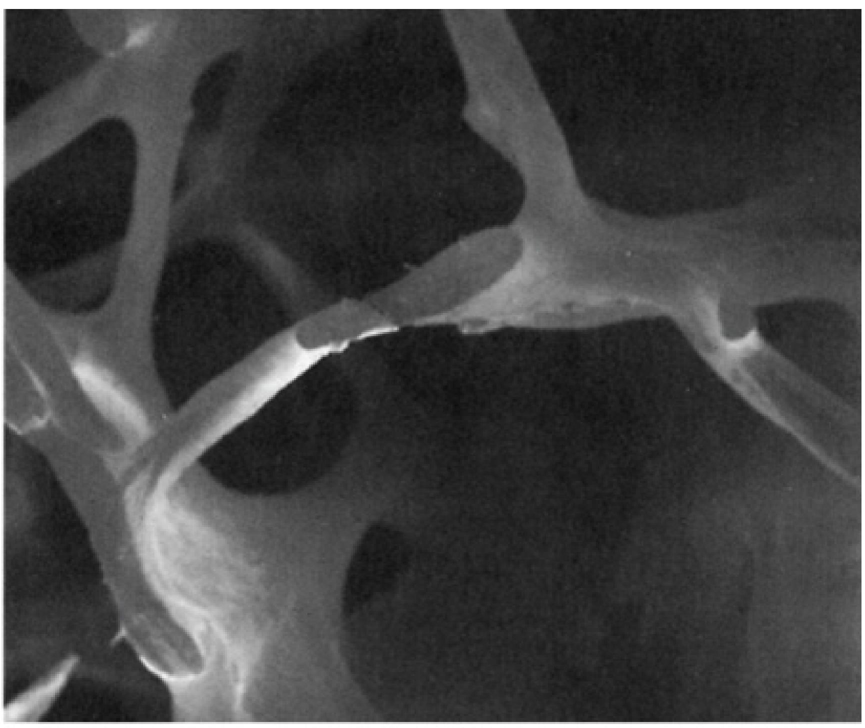
TREATMENT INDICATIONS

The primary goal of osteoporosis treatment is fracture prevention in women who have low bone mineral density (BMD) or additional risk factors for fracture (Fig. 22-1). Toward this end, therapy aims to stabilize or increase BMD. Treatment includes lifestyle changes and often pharmacologic therapy.

FIGURE 22-1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Electron micrographs of tissue obtained from iliac crest biopsy. Normal bone architecture is seen in the biopsy from an individual with normal bone mineral density (**top**). Diminished bone architecture is seen in the biopsy from an individual with osteoporosis (**bottom**). *(From Dempster, 1986, with permission.)*

Several organizations offer guidelines for intervening with pharmacologic therapy (Table 22-4). The National Osteoporosis Foundation (NOF) and American Association of Clinical Endocrinologists (AACE) state that initiation of pharmacologic therapy should be considered for all postmenopausal women with T-scores less than â€“2.0 without other risk factors, or for those with T-scores less than â€“1.5 if other risk factors are present (see Table 21-6). Guidelines from the NOF also recommend initiating therapy to reduce fracture risk in women with a prior vertebral or hip fracture. Alternatively, the North American Menopause Society (NAMS) recommends starting therapy for: (1) all postmenopausal women with total hip or spine T-scores at or below â€“2.5, (2) for those with an osteoporotic vertebral fracture, and (3) all postmenopausal women with total hip or spine T-scores from â€“2.0 to â€“2.5 who have one or more additional risk factors for fracture.

Table 22-4 Thresholds for Initiation of Pharmacologic Therapy for Bone Fracture Prevention

	Without Risks (T-scores)	**With Risks (T-scores)**	**Prior Fracture**
NOF	<â€“2.0	<â€“1.5	Initiate therapy
AACE	<â€“2.0	<â€“1.5	N/A
NAMS	≤â€“2.5	â€“2.0 toâ€“2.5	Initiate therapy

AACE = American Association of Clinical Endocrinologists; N/A = not applicable; NAMS = North American Menopause Society; NOF = National Osteoporosis Foundation.

PHARMACOLOGIC CONSIDERATIONS

Drugs prescribed for fracture prevention attempt to restore and balance bone remodeling by reducing bone resorption or by stimulating bone formation. However, improvement in BMD with therapeutic intervention varies according to the composition of the bone. Therapies that prevent bone resorption will act most quickly on bone that has high trabecular content and rapid turnover, such as the vertebrae. In contrast, the impact of drug therapies on the hip may be delayed because the hip is composed of approximately 50 percent trabecular and 50 percent cortical bone (see Fig. 21-7).

Therapeutic options include hormone therapy (HT) for the prevention of osteoporosis, and bisphosphonates and selective estrogen receptor modulators (SERMs) for prevention *and* treatment. Additionally, calcitonin and an injectable recombinant human parathyroid hormone (PTH) have been approved for treatment. Of these, PTH is the first FDA-approved agent that works by stimulating bone formation rather than slowing bone resorption.

HORMONAL THERAPY

Estrogen and Progesterone Replacement

As estrogen levels decline, bone-remodeling rates increase and favor bone resorption over bone formation. Results from more than 50 randomized, placebo-controlled trials show HT reduces the rate of bone resorption and results in an increase in BMD (North American Menopause Society, 2002). The WHI demonstrated that therapy with estrogen plus progesterone prevents vertebral fractures in postmenopausal women not known to have osteoporosis (The Women's Health Initiative Steering Committee, 2004). This is the first study to show that an antiresorptives can reduce the incidence of hip fracture.

Unfortunately, this preventive effect is lost rapidly following discontinuation of HT (Barrett-Connor, 2003). Women participating in the National Osteoporosis Risk Assessment (NORA) trial who had discontinued estrogen therapy within the 5 years preceding the study demonstrated a significantly higher hip fracture risk than did women who had never received estrogen therapy (odds ratio 1.69; 95 percent CI 1.08 to 2.66).

Selective Estrogen Receptor Modulators

These oral drugs are nonhormonal compounds that bind to the estrogen receptor but induce different estrogenic responses in various tissues. For example, raloxifene (Evista, Eli Lilly) is the only selective estrogen receptor modulator (SERM) approved for the prevention and treatment of osteoporosis. It activates estrogen receptors in the bone but does not appear to activate those in the breast or uterus.

Raloxifene may be most appropriate for prevention and treatment of vertebral disease. For example, raloxifene prevented vertebral fractures in the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, which enrolled 7,705 postmenopausal women with osteoporosis. The beneficial effects of raloxifene, 60 mg/d, appeared rapidlyâ€"clinical vertebral fracture risk was reduced by 68 percent following the first year of therapy. In addition, this effect was sustained over time. At 4 years of treatment, dosages of 60 mg daily led to a 36-percent reduction in fractures, and 120 mg each day produced a 43-percent decline (Delmas, 2002; Ettinger, 1999). However, in the MORE trial, Ettinger reported that raloxifene therapy compared with placebo was not associated with significant reductions in nonvertebral fracture risks at 3 and 4 years.

In addition to its bone effects, raloxifene may protect against breast cancer, as suggested by observational studies of various clinical trials (Barrett-Connor, 2006). The incidence of breast cancer was evaluated as a secondary end point in the MORE trial. Investigators found that raloxifene was associated with a 65-percent relative risk reduction in all breast cancers. Of specific breast cancer subtypes, they noted a 90-percent reduction in estrogen receptorâ€"positive cancers, a 12-percent reduction in estrogen receptorâ€"negative breast cancers, and a 76-percent relative risk reduction in invasive breast cancer.

Raloxifene may not have the same increased cardiovascular risk profile as estrogen. In a MORE post hoc analysis, 4 years of raloxifene therapy had no adverse effect on cardiovascular events in the overall cohort. Advantageously, it did result in a significant 40-percent reduction in the incidence of cardiovascular events among a subgroup of women with increased cardiovascular risk (Barrett-Connor, 2002).

Of side effects, hot flushes are associated with raloxifene therapy, although the incidence is low (Cohen, 2000). Furthermore, raloxifene, 60 mg daily for 4 years, has been associated with an increased risk of thromboembolic events (RR 1.78, 95 percent CI 0.99 to 3.19). In one study, the relative risk associated with any dosage of raloxifene was 2.76 for deep vein thrombosis, 2.76 for pulmonary embolism, and 0.50 for retinal vein thrombosis (Delmas, 2002).

NONHORMONAL ANTIRESORPTIVE AGENTS

Currently there are two main types of nonhormonal pharmacologic agents: (1) those that primarily act by inhibiting resorption, termed *antiresorptives* , and (2) those that act by increasing bone formation, termed *anabolic agents* . Most of the bone-active agents currently available in the United States inhibit bone resorption. Estrogen and SERMs as well as bisphosphonates, calcitonin, and vitamin D each have anitresorptive properties. All have been shown to halt bone loss, and most also increase BMD.

Bisphosphonates

Three bisphosphonates are currently available and include alendronate (Fosamax, Merck&Co., Whitehouse Station, NJ), risedronate (Actonel, Proctor and Gamble Pharmaceuticals, Cincinnati, OH), and ibandronate (Boniva, Roche Pharmaceuticals, Nutley, NJ) (Table 22-5). A fourth bisphosphonate, zoledronate (Zometa, Novartis, East Hanover, NJ), is a potent bisphosphonate that has been approved as an intravenous infusion for malignancy-associated hypercalcemia treatment. Currently, it is undergoing a phase III clinical trial for the treatment of postmenopausal osteoporosis as an intravenous infusion once annually (Colon-Emeric, 2004; Lambrinoudaki, 2006).

Table 22-5 Agents Approved in the United States for the Management of Osteoporosis

Agents (Brand Name)	Dosage	FDA-Approved Indications
Bishosphonates		
Risedronate (Actonel)	5 mg orally daily 35 mg orally weekly	Prevention or treatment of postmenopausal osteoporosis
	5 mg orally daily	Treatment of glucocorticoid-induced osteoporosis
Alendronate (Fosamax)	5 mg orally daily 35 mg orally weekly	Prevention of postmenopausal osteoporosis
	10 mg orally daily	Treatment of postmenopausal osteoporosis
	70 mg orally weekly	
	5 mg orally daily (10 mg orally daily in postmen-opausal women not receiving estrogen)	Treatment of glucocorticoid-induced osteoporosis
Ibandronate (Boniva)	2.5 mg orally daily 150 mg orally monthly	Prevention or treatment of postmenopausal osteoporosis
Hormones		
Conjugated equine estrogen	0.625 mg orally daily	Prevention of postmenopausal osteoporosis
Various estrogen preparations	See Table 22-2	Prevention of postmenopausal osteoporosis
Recombinant human (PTH)		
Teriparatide (Forteo)	20 μgSC daily	Treatment of postmenopausal osteoporosis
SERM		
Raloxifene (Evista)	60 mg orally daily	Prevention or treatment of postmenopausal osteoporosis
Salmon calcitonin	200 IU intranasally daily (alternating nostrils daily)	Treatment of postmenopausal osteoporosis
	100 units SC or IM every other day	

FDA = Food and Drug Administration; IM = intramuscularly; PTH = parathyroid hormone: SC = subcutaneously; SERM = selective estrogen receptor modulator.

Modified from Zizic, 2004, with permission.

Bisphosphonates display poor bioavailability, and therefore should be taken on an empty stomach with adequate water for proper dissolution and absorption. In general, these agents have a favorable overall safety profile, and adverse event rates are comparable with placebo (Black, 1996; Harris, 1999). However, bisphosphonates may cause upper gastrointestinal (GI) inflammation, ulceration, and bleeding (Lanza, 2000). Thus, to aid delivery to the stomach and reduce the risk of esophageal irritation, dosing instructions should be reinforced with each patient. First, bisphosphonates should be taken in the morning with a full glass of water. During the 30 minutes following administration, no other food or beverages should be consumed. Finally, women must remain upright (sitting or standing) for at least 30 minutes after ingesting the drug.

In addition to GI effects, recently bisphosphonate use has been linked with osteonecrosis of the jaw (ONJ), especially following dental extractions (Marx, 2003; Srinivasan, 2007). Fortunately, this complication is rare with oral bisphosphonates (Ruggiero, 2004). More commonly, ONJ is seen with intravenous zoledronate use in those with malignancy-related bone disease (Woo, 2006).

Alendronate

This bisphosphonate is approved for the treatment and prevention of osteoporosis. Alendronate has been shown to reduce the risk of vertebral fractures in postmenopausal women with low BMD or osteoporosis, either with or without existing vertebral fractures (Table 22-6) (Black, 1996). Alendronate also reduces nonvertebral fracture risk in women with osteoporosis. Among women with osteoporosis who participated in the Fracture Intervention Trial (FIT), the risk of nonvertebral fractures was reduced by month 24. In addition, the effects of alendronate are sustained. For example, women who used alendronate for 5 years and then discontinued use for a subsequent 5 years had comparable nonvertebral fracture rates as women using the drug for 10 years (Black, 2006; Bone, 2004).

Table 22-6 Summary of Major Clinical Trials of Bisphosphonates in Women with Postmenopausal Osteoporosis

			Relative Reduction of Fracture Risk for Active Treatment versus Placebo	
Trial	**Inclusion Criteria (number of patients in the trial)**	**Dosage**	**Vertebral Fractures**	**Nonvertebral Fractures**
Risedronate (Actonel)				
VERT	Two or more vertebral fractures or one vertebral fracture and a T-score of â€“2.0 or lower (2,458)	5 mg daily	65% reduction after 1 yr ($p < .001$) 41% reduction after 3 yrs ($p = .003$)	NR 39% reduction after 3 yrs ($p = .02$)
VERT	Two or more vertebral fractures (1,226)	5 mg daily	61% reduction after 1 yr ($p = .001$) 49% reduction after 3 yrs ($p < .001$)	NR 33% reduction after 3 yrs ($p = .06$)
HIP	Osteoporosis or one or more risk factors for osteoporosis (9,331)	2.5 and 5 mg daily	NR	20% reduction after 3 yrs ($p = .03$)
Alendronate (Fosamax)				
FIT	Low femoral-neck BMD (4,432)	5 mg daily for 2 yrs followed by 10 mg daily for 2 yrs	44% reduction after 4 yrs ($p = .001$)	12% reduction after 4 yrs ($p = .13$)

FIT	Low femoral-neck BMD plus one or more clinical vertebral fractures (2,027)	5 mg daily for 2 yrs followed by 10 mg daily for 1 yr	47% reduction after 3 yrs (p <.001)	20% reduction after 3 yrs (p =.063)
Alendronate Phase III Osteoporosis Treatment Study	Osteoporosis (994)	5 or 10 mg daily for 3 yrs 20 mg daily for 2 yrs followed by 5 mg daily for 1 yr	48% reduction after 3 yrs, based on pooling of all data (p =.03)	21% reduction after 3 yrs (p values not reported; not significant)

BMD = bone mineral density; FIT = Fracture Intervention Trial; IHP = Hip Intervention Program; NR = not reported; VERT = Vertebral Efficacy with Risedronate Therapy.

Adapted from Zizic (2004), with permission.

Risedronate

This bisphosphonate is an effective agent in the prevention and treatment of postmenopausal osteoporosis. The strongest data supporting its efficacy stem from the Vertebral Efficacy with Risedronate Therapy (VERT) trials, conducted multinationally and also in North America. In the VERT multinational trial, Reginster and co-workers (2000) showed that risedronate reduced the risk of new vertebral fractures by 61 percent at 1 year and by 49 percent at 3 years of use. Moreover, both VERT trials found significant reductions in vertebral fractures as early as 6 months after initiation of risedronate therapy (Roux, 2004). Two extensions of these trials have provided evidence of sustained efficacy. The continuation of risedronate therapy for 2 additional years (5 years total) in the multinational VERT study was associated with a 59-percent reduction in new vertebral fractures compared with placebo.

Ibandronate

This newer bisphosphonate is approved for the prevention and treatment of postmenopausal osteoporosis. Ibandronate is an effective agent, and data from the Oral Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe (BONE) trial showed that daily ibandronate lowered incident vertebral fracture risk by 62 percent (Chesnut, 2004). To improve compliance, this drug was evaluated as a once-monthly therapy. Once-monthly oral ibandronate is at least as effective and well tolerated as daily treatment (Miller, 2005; Reginster, 2006). Moreover, once-monthly administration may be more convenient and thereby improve compliance rates.

Calcitonin

The polypeptide hormone calcitonin decreases the rate of bone absorption by inhibiting resorptive activity in osteoclasts. Calcitonin is a protein and as such, oral administration leads to its digestion. For this reason, it is delivered as an injection or nasal spray (Fortical, Upsher-Smith, Minneapolis, MN; Miacalcin, Novartis, East Hanover, NJ) (see Table 22-5). Salmon calcitonin nasal spray has been associated with a reduction in vertebral fracture risk among postmenopausal women with osteoporosis. In the Prevent Recurrence of Osteoporotic Fractures (PROOF) study, calcitonin nasal spray, 200 IU administered daily for up to 5 years, reduced the risk of vertebral fractures by 33 percent compared with placebo. However, vertebral fracture reduction was not seen at lower (100 IU/d) or higher (400 IU/d) dosages (Chesnut, 2000). Moreover, in this study, calcitonin failed to produce significant reductions in nonvertebral fracture.

Some observational data suggest that calcitonin has an analgesic effect independent of its effect on bone (Hauselmann, 2000; Ofluoglu, 2007). This analgesic effect may make this agent particularly useful as an adjunct to other therapies for osteoporosis in women with painful, symptomatic fracture (Blau, 2003). Injectable or intranasal calcitonin is associated with an 8- to 10-percent incidence of nausea or gastric discomfort and a 10-percent incidence of local site reactions. These symptoms tend to decrease in severity with continued use. Nasal symptoms such as rhinitis occur in 3 percent of patients treated with intranasal calcitonin (Cranney, 2002).

PARATHYROID HORMONE

Recombinant parathyroid hormone (PTH 1â€“34), known as teriparatide, is given by subcutaneous injection and is approved by the FDA for the treatment of postmenopausal women with established osteoporosis, who are at high risk for fracture. Teriparatide (Forteo, Eli Lilly) increases osteoblast numbers and activity by recruiting new cells and reducing apoptosis of differentiated osteoblasts. At low daily doses of teriparatide, the anabolic effects of PTH predominate. This is in contrast to the catabolic effects generally associated with long-term, higher-dose, and chronic exposure to PTH.

Clinical studies indicate that teriparatide increases bone quality by increasing bone density, turnover, and size (Rubin, 2002). Moreover, improvements in microarchitectural elements are evident in both cancellous and cortical regions. In women with postmenopausal osteoporosis, teriparatide, 20 or 40 µg/day, administered for approximately 21 months, was associated with 65-percent and 69-percent reductions in vertebral fractures, and 35-percent and 40-percent reductions in nonvertebral fractures, respectively (Neer, 2001).

Similar findings were reported in a study of 52 women treated with concomitant teriparatide and HT compared with HT alone (Lindsay, 1997). In this study, at the end of 3 years, increases in spine, total hip, and total body BMD were 13.4 percent, 4.4 percent, and 3.7 percent, respectively, in the combined treatment group. The addition of alendronate to teriparatide, however, does not appear to enhance effects on BMD (Gasser, 2000). The effects of combination use of PTH with other bisphosphonates are not known.

In general, PTH is safe and well tolerated, although additional data from long-term studies are needed. The most frequent treatment-related adverse events in clinical trials of teriparatide were dizziness, leg cramps, nausea, and headache. Toxicity studies with rats have shown an increased risk of osteosarcoma, but as there are significant differences in bone metabolism between rats and humans, it is unlikely that the rat data are applicable to humans. However, a black box warning has been included on the product labeling in the United States, and use of teriparatide should be avoided by patients at increased risk for skeletal malignancy. Use for more than 2 years is not recommended due to the potential of side effects (Tashjian, 2002).

Other anabolic agents have been or are currently being studied for use in the treatment of osteoporosis and include fluoride, growth hormone, insulin-like growth factor-1, androgen, tibilone, strontium, and statins. Full-length PTH (PTH 1â€“84) is also currently under investigation (Greenspan, 2007; Rubin, 2002).

NONPHARMACOLOGIC THERAPY

Nonpharmacologic interventions are important cornerstones of osteoporosis prevention. They include dietary modifications, exercise programs, fall prevention strategies, and education.

Calcium

For bone maintenance, adequate daily calcium intake is essential. For women between 31 and 50 years, the recommended dietary reference intake (DRI) is 1,000 mg each day, whereas 1,200 mg is suggested for those 51 years and older (Institute of Medicine, 2002). Few meet these goals, and calcium deficiency is widespread. For example, more than

90 percent of women fail to take in enough calcium through their diets to meet DRIs put forth by the Food and Nutrition Board of the Institute of Medicine. Although poor calcium intake is observed at all ages, it appears to be most common among older individuals. Specifically, less than 1 percent of women 71 years or older actually meet recommended goals.

Calcium supplementation combined with vitamin D administration have been associated with reduced bone loss and decreased risk for fractures in a number of prospective studies (Chapuy, 1992; Dawson-Hughes, 1997; Larsen, 2004). However, supplementation must be continued long term for efficacy to be sustained.

Vitamin D

The DRI of vitamin D is 400 IU/d for those aged 51 to 70 years, and 600 IU/d for those older than 70. As with calcium, the prevalence of vitamin D deficiency is high, especially in the elderly. It leads to poor calcium absorption, secondary hyperparathyroidism, increased bone turnover, increased rates of bone loss, and if severe, impaired bone mineralization. In addition, vitamin D deficiency causes muscle weakness and is associated with an increase in rates of falls.

Vitamin D supplementation can reverse many of these effects and significantly reduce falls and hip fractures. Although a large study of patients aged 70 years and older failed to demonstrate a decrease in hip fractures using 400 IU/d of vitamin D for 3 years, other studies using approximately 800 IU/d of vitamin D have demonstrated fracture protection (Dawson-Hughes, 1997). These findings suggest that doses higher than the current DRI for vitamin D may be necessary for anti-fracture efficacy.

Diet

A relationship between protein intake and BMD has been reported, but a relationship with fractures has not been described. Using data from the Third National Health and Nutrition Examination Survey (NHANES III), Kerstetter and colleagues (2000) demonstrated a significant association between protein intake and total femur BMD among non-Hispanic white women aged 50 years and older. Moreover, protein supplementation (20 g/d) 5 times weekly for 6 months following hip fracture was associated with a 50-percent reduction in femoral bone loss at 1 year compared with placebo.

Although no specific recommendations regarding protein intake can be made based on the limited data available, it seems prudent for clinicians to ensure that their patients eat healthy diets that provide the daily DRI of protein. As put forth by the Institute of Medicine, diets should contain at least 46 g/d for women (Dawson-Hughes, 2002). There may be upper limits for desirable protein intake as well. Excess urinary calcium excretion has been observed in association with the large acid loads delivered by very-high-protein diets (Barzel, 1998). Although it is not yet proven, there is concern that these calcium losses may jeopardize bone strength.

Caffeine consumption does not appear to influence bone health in healthy postmenopausal women who maintain an adequate daily intake of calcium and vitamin D. However, one longitudinal study showed that even moderate amounts of caffeine (2 to 3 servings of coffee per day) may lead to bone loss in women with low calcium intake (less than 800 mg/d) (Harris, 1994).

Calcium reabsorption is directly proportional to sodium reabsorption in the renal tubule. Accordingly, increases in dietary sodium have been observed to cause increases in urinary calcium excretion and corresponding increases in biochemical markers of bone turnover. Specifically, a relationship between high sodium intake (more than 1,768 mg daily) and lower bone density has been described (Sellmeyer, 2002). This sodium effect appears to be independent of calcium intake and activity levels. As with caffeine, it would be considered practical for all women to moderate sodium intake as a precautionary measure until this relationship is fully understood.

Physical Activity

Small but statistically significant increases in BMD have been observed in postmenopausal women participating in exercise programs, including aerobic exercise and resistance training (heavy weight with few repetitions). A recent meta-analysis of 18 randomized, controlled trials concluded that aerobic, weight-bearing, and resistance exercise were all effective in increasing BMD of the spine. Of these, walking was observed to benefit BMD of both the spine and the hip, and aerobic exercise also increased wrist BMD (Bonaiuti, 2002).

Although an increase in bone density may occur, especially at the sites at which the exercise is directed, it is important to note that the benefits of exercise are likely to be due to factors other than changes in BMD (Carter, 2002). For example, an association between exercise and reduced falls has been reported. Improvements in balance, stronger muscles, better muscle tone, and stronger more flexible bone, all undoubtedly contribute to fracture reduction.

FALL-PREVENTION STRATEGIES

Falls are responsible for more than 90 percent of hip fractures (Carter, 2002). Sideways falls appear to be the most detrimental and were independently associated with hip fracture in a study by Greenspan and associates (1998). Therefore, fall prevention is essential for women with osteopenia or osteoporosis. Living conditions should be modified to minimize falls by reducing clutter and implementing nonslip tiles, rugs with nonskid backing, and night lights.

Hip protector padding was also initially thought to reduce hip fractures in elderly adults. However, a recent analysis of the Cochrane database by Parker (2003) indicates that the effectiveness of hip protectors may be less certain, and compliance remains low. Falls and fractures often occur at night, when women are likely to have taken off their hip protectors. This may result from the bulkiness of hip protectors, which are uncomfortable to wear while sleeping (van Schoor, 2003).

Treatment of Sex-Related Issues

DYSPAREUNIA

Estrogen Replacement

Low estradiol levels commonly lead to vaginal atrophy or dryness and subsequent dyspareunia. Data from the Yale Midlife Study showed a close relationship between serum estradiol level and sexual problems. In this study, significantly more women with estradiol levels less than 50 pg/mL reported vaginal dryness, dyspareunia, and pain compared with women whose estradiol levels were greater than 50 pg/mL (Sarrel, 1998). Prospective records of coital behavior and concomitant steroid analysis revealed that women with estradiol levels less than 35 pg/mL reported significant reductions in coital activity.

Estrogen replacement effectively reverses atrophic changes. Of these, vaginal atrophy and diminished vaginal mucosal elasticity, vaginal fluid secretion levels, blood flow, and sensorimotor responses are improved by either topical or systemic estrogen (Dennerstein, 2002). Moreover, a meta-analysis evaluated randomized, controlled trials from 1969 to 1995 investigators found, that compared with placebo, oral or vaginal estrogens significantly improved vaginal atrophy symptoms, dyspareunia, and vaginal pH (Cardozo, 1998). If oral and vaginal estrogens were compared, vaginal products had greater patient acceptance, lower systemic estradiol concentrations, yet significant improvement of dyspareunia and pH changes.

Of vaginal topical agents, available forms include creams, continuous-release rings, and tablets (Table 22-7). In comparing types during a 12-week study period, Ayton and colleagues (1996) found that a continuous low-dose estradiol-releasing vaginal ring (Estring, Pfizer, New York, NY) provided comparable relief to CEE vaginal cream used during 12 weeks. In addition, study patients found the vaginal ring significantly more acceptable than the cream. The ring is prescribed as a single unit. Each unit contains 2 mg of estradiol and is worn vaginally for 90 days and then replaced.

Table 22-7 Selected Estrogen Vaginal Preparations for the Treatment of Menopausal Vaginal Symptoms

Preparation	Generic Name	Brand Name	Dose
Vaginal cream	Conjugated estrogens	Premarin	0.625 mg per 2 g cream: 2 g daily for 2 weeks, then 1â€“2 g 2 to 3 times weekly
	17β-estradiol	Estrace	0.1 mg per 2 g cream: 2 g daily for 2 weeks, then 1â€“2 g 2 to 3 times weekly
Vaginal tablet	Estradiol hemihydrate	Vagifem	0.025 mg per tablet: 1 tablet daily for 2 weeks, then 1 tablet twice weekly
Vaginal ring	17α-estradiol	Estring	0.0075 μg daily (inserted every 90 days)

Most products listed in Table 22-2 for the treatment of menopausal hot flushes are also approved for the treatment of vaginal dryness.

From Grady, 2006, with permission.

Alternatively, a 25-μg 17β-estradiol tablet (Vagifem, Novo Nordisk Pharmaceuticals, Princeton, NJ) is available for vaginal application. One tablet is inserted daily for an initial 2 weeks of treatment, and is followed by twice-weekly application. These tablets and CEE vaginal cream have been found to be equivalent in relieving symptoms of atrophic vaginitis (Rioux, 2000). Advantageously, women using vaginal tablets had less endometrial proliferation or hyperplasia than those using cream. Additionally, tablets were rated significantly more favorable than the cream, and their use was associated with fewer patient withdrawals from the study.

Vaginal Lubricants and Moisturizers

A variety of water-soluble vaginal lubricants are available over the counter for treatment of vaginal dryness with coitus. Alternatively, a polycarbophil-based gel (Replens, Lil' Drug Store Products, Cedar Rapids, IA) offers a more sustained correction of vaginal dryness symptoms. This gel is an acidic hydrophilic insoluble polymer, which can hold water to act as a vaginal moisturizer. The polymer binds to the vaginal epithelium and is sloughed with epithelial layer turnover. In addition, the acidity of the gel helps to lower the vaginal pH to that found in premenopausal women.

LIBIDO

Estrogen Replacement

A randomized, double-blind crossover clinical trial showed significant positive effects of estrogen on mood and sexuality. A 12-month study of 49 women who had undergone oophorectomy reported a significant positive effect of estrogen on both mood and sexuality, apart from vaginal symptomatology. This 12-month trial had four 3-month arms with no washout period: (1) ethinyl estradiol (50 μg), (2) levonorgestrel (250 μg), (3) a combination of these two agents, and (4) placebo. Of these, ethinyl estradiol showed a significant positive effect on mood and sexual desire, enjoyment, and orgasmic frequency. There were no differences between groups in coital rate (Dennerstein, 2002).

Testosterone

Androgen replacement in women with hypoactive sexual desire disorder is a controversial topic. Although studies have documented an association between androgen replacement and improved sexual desire, large, quality trials with long-term follow-up are needed (Pauls, 2005). Shifren and colleagues (2000) demonstrated that women who underwent surgical menopause and who were subsequently treated with systemic estrogen had improved sexual function and psychological well-being if 300 μg of transdermal testosterone was concurrently delivered. However, there was a strong placebo response in this study, and many subjects had evidence of borderline-high androgen levels. Lobo and colleagues (2003) evaluated postmenopausal women to assess effects on hypoactive sexual desire disorder of 0.625 mg oral estrogen with or without 1.25 mg methyltestosterone. At a 16-week re-evaluation, therapy with methyltestosterone increased bioavailable testosterone and improved sexual interest and desire in most women.

Symptoms of androgen insufficiency include diminished sense of well-being, persistent fatigue, sexual function changes, and low levels of serum-free testosterone. Women with these findings may be offered replacement. Importantly, candidates should be counseled that most androgen replacement therapy is off-label and not U.S. FDA-approved. Moreover, most of the available data are based on short-term studies and long-term safety and efficacy are unknown (Braunstein, 2007). Therapy should be performed under close clinician supervision.

Early effects of androgen therapy include acne and hirsutism, with a recent study reporting a 3-percent increased rate of acne in testosterone-therapy groups (Lobo, 2003). Long-term side effects such as male pattern baldness, voice deepening, and clitoral hypertrophy are infrequent within normal androgen levels. Androgen therapy may adversely affect the lipid profile, and knowledge about long-term effects on cardiovascular risk is unknown (Davis, 2000).

Potential benefits of androgen include increased muscle mass and stimulation of bone formation as well as diminished hot flush frequency (Table 22-8) (Notelovitz, 2002). With therapy, levels of androgens, lipids, and liver enzymes initially should be performed at 1- to 2-month intervals. Restoration to the upper half of the normal androgen range is necessary to ensure a good therapeutic response (see Table 15-4). (Munarriz, 2002).

Table 22-8 Benefits of Testosterone Treatment for Women		
Indication	**Possible Benefit**	**Formulations**
Bone strength	Increase bone mineral density	Oral, supraphysiologic doses
Cognitive or psychological	Protective of memory, improved sense of well-being	Physiologic doses
Sexual dysfunction	Increase desire/interest, frequency Increase frequency, satisfaction, orgasm Increase desire, orgasm Increase frequency and pleasure	Oral Implants Intramuscular, supraphysiologic dose Transdermal

From Margo, 2006, with permission.

Currently the only FDA-approved testosterone preparation for women is methyltestosterone combined with esterified estrogen, suitable only for postmenopausal patients. A list of available testosterone preparations is shown in Table 22-9. Phase II trials have been carried out for a testosterone gel and testosterone patch, but FDA approval is delayed, waiting on longer-term safety and efficacy trials.

Table 22-9 Selected Androgens for Treatment of Menopausal Symptoms			
Brand Name	**Generic Name**	**Dosage**	**Manufacturer**
Oral androgen			
Halotestin	Fluoxymesterone	2 mg	Pfizer
Estrogen-androgen combinations			
Estratest	Esterified estrogens	1.25 mg	Solvay
	Methyltestosterone	2.5 mg	
Estratest HS	Esterified estrogens	0.625 mg	Solvay
	Methyltestosterone	1.25 mg	
Depo-Testadiol injection	Estradiol cypionate	2 mg	Pfizer
	Testosterone cypionate	50 mg	

Treatment of Depression

Major and minor depression are the two most prevalent forms of acute depressive illness in women (see Chaps. 13, Mood Disorder Prevalence). Although some controlled studies have shown improvement in mood with estrogen treatment, it is recommended that estrogen should not be used as a primary treatment for women with depression. First-line treatment for menopausal women presenting with depression would be a traditional antidepressant, such as a selective serotonin reuptake inhibitor (SSRI). However, treatment with estrogen for certain women who have mild to moderate depression may be selected as an alternative. Consideration may be given to those who fail to respond to a conventional first-line intervention, those who refuse to take psychotropic agents, or those who will begin HT for other acute menopausal symptoms and who could delay antidepressant therapy until determining whether estrogen treatment is sufficient.

Treatment of Skin Aging

As people age, their skin elasticity decreases and strong collagen fibers weaken. In addition, fatty tissue and collagen beneath the skin shrinks. As a result, the skin lays more loosely, and lines appear where the facial muscles attach to the skin's undersurface. Many factors play a role in the rate and degree of the aging. First and foremost is genetics. People with thin, dry, fair skin will realize signs earlier. In addition, overexposure to sunlight and excessive use of tobacco and alcohol accelerate skin aging. Thus, prevention of skin aging includes protection from ultraviolet (UV) light, avoidance of tobacco, and limitation of alcohol intake.

Skin is a hormonally sensitive structure, and both estrogen and androgen receptors have been localized to skin (Hasselquist, 1980; Schmidt, 1990). However, it is difficult to separate hormonal deficiency from chronological skin aging and age-related environmental insults such a smoking or photo-aging secondary to sun exposure.

The predominant evidence for an estrogen effect on skin has been derived from observational studies using various estrogen preparations with or without cyclic progestin. Thus, it is difficult to clearly separate the effects of estrogen from estrogen and progestin in many of the studies. There have been only two randomized, double-blinded, placebo-controlled trials that have examined the effects of estrogen therapy (ET) or hormone therapy on skin. Both trials suggest that ET increases dermis thickness, whereas HT can increase skin collagen fibers (Maheux, 1994; Sauerbronn, 2000). With few randomized studies addressing this topic, the American College of Obstetricians and Gynecologists (2004) states that "there is insufficient evidence to recommend estrogen treatment to increase skin thickness and collagen content and thereby decrease wrinkling in sun-exposed areas such as the face and forearms."

PREVENTIVE HEALTH CARE

Leading causes of morbidity and mortality for women older than 40 are found in Tables 22-10 and 22-11. Testing and prevention strategies are aimed at reducing the incidence and effects of these causes. In addition to testing, illness prevention requires patient education to enable women to play an active role in maintaining their own health. Through dialogue and counseling, clinicians and their actively participating patients can reap the benefits of preventive care. Although prevention recommendations for many of these causes of morbidity are reviewed in Chapter 1, a select few found commonly in older populations are discussed below.

Table 22-10 Leading Causes of Mortality in Older Women[a]
In those between 40 and 64 years:
Cancer
Heart disease
Cerebrovascular disease
Motor vehicle accident
Chronic obstructive pulmonary disease
Diabetes mellitus
In those older than 65 years:
Heart disease
Cancer
Cerebrovascular disease
Chronic obstructive pulmonary disease
Pneumonia and influenza
Diabetes mellitus
Motor vehicle accident

[a] For each age group, causes are listed by their descending frequency.

Table 22-11 Leading Causes of Morbidity for Women Older Than 40 Years[a]
Arthritis
Asthma
Back pain
Cancer
Cardiovascular disease
Chronic obstructive pulmonary disease
Depression
Diabetes mellitus
Headache or migraine
Hypertension
Menopause
Mental disorders
Respiratory infections
Obesity
Osteoporosis
Pneumonia
Sexually transmitted diseases
Skin conditions
Ulcers
Urinary tract infection
Vertigo
Vision impairment

[a] Listed alphabetically.

Prevention of Alzheimer Senile Dementia

Dementia is defined as a progressive decline in intellectual and cognitive function. Its causes can be categorized into three broad groups: (1) cases in which the brain is the target of a systemic illness; (2) primary structural causes such as tumor; and (3) primary degenerative diseases of the nervous system, such as senile dementia of the Alzheimer type (SDAT). It is estimated that up to 50 percent of women aged 85 years or older may suffer from senile dementia or SDAT.

Early signs of dementia may be subtle. In compensation, women commonly restrict their spheres of activity so that they continue to function well. Consequently, dementia may not become apparent until a woman attempts to function in a broader context. In these instances, she may become lost or show significant confusion.

Prevention or delay of senile dementia includes screening for and early treatment of reversible causes of dementia. Identification and treatment of systemic illness such as vitamin B12 deficiency, hypothyroidism, opportunistic infections such as cryptococcosis in immunocompromised hosts, and thiamine deficiency may reverse some forms of dementia. Central nervous system complications

of syphilis are rare. However, in those with acquired immune deficiency syndrome (AIDS), the frequency of tertiary syphilis has been rising.

The role of estrogen in the prevention of dementia is controversial. Several epidemiologic studies have suggested that HT prevents development of SDAT. Moreover, meta-analyses of observational studies found that HT was associated with a decreased risk of dementia (Yaffe, 1998). However, data from a large randomized double-blind placebo-controlled study found negative findings for a preventive role. Women enrolled in the Women's Health Initiative Memory Study (WHIMS), an ancillary study of the WHI, were noted to have increased rates of dementia compared with those given placebo (Shumaker, 2003, 2004). Unfortunately, these mixed findings leave unanswered questions regarding HT's efficacy in preventing dementia in postmenopausal women. Currently, HT is not recommended for this indication.

Prevention of Dental Disease Related to Menopause

Dental disease and tooth loss may be an indicator of osteoporosis. Maintenance of good dental hygiene and good bone mineral density will help retard dental disease associated with aging.

Prevention of Urogynecologic Disease

The development of pelvic organ prolapse and urinary incontinence is multifactorial. Thus, the effectiveness of preventive measures such as cesarean delivery, pelvic floor muscle training (Kegel exercises), and estrogen therapy is unclear. Estrogen receptors are found throughout the lower urinary and reproductive tracts. In these areas, hypoestrogenism is associated with collagen changes and diminished vascularity of the urethral subepithelial plexus. However, separating the effects of hypoestrogenism from aging in the genesis of pelvic organ prolapse and urinary incontinence is problematic and discussed in Chapters 23 and 24.

For a woman with obvious lower reproductive tract atrophic changes, a trial of vaginal estrogen treatment for urinary incontinence is reasonable. However, several studies evaluating effects of estrogen have noted either de novo development or worsening of incontinence in women using HT (Hendrix, 2005; Jackson, 2006). Accordingly, there is no current indication for the use of HT for the prevention of pelvic organ prolapse or incontinence.

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DEFINITIONS

Urinary incontinence is defined as involuntary leakage of urine. In addition to the urethra, urine can also leak from an extra-urethral source, such as fistulas or congenital malformations of the lower urinary tract. Although a number of different forms of incontinence exist, this chapter will focus on the evaluation and management of stress and urge incontinence.

According to International Continence Society guidelines, urinary incontinence is a symptom, sign, as well as a condition (Abrams, 2002). For example, with *stress urinary incontinence* (SUI), a patient may complain of involuntary urine leakage on exertion or with sneezing or coughing. Concurrently with these events, involuntary leakage from the urethra synchronous with these events may be a documented sign noted by a provider. And as a condition, incontinence is objectively demonstrated during urodynamic evaluation if involuntary leakage of urine is seen with increased abdominal pressure and absence of detrusor contraction. Under these circumstances, when the symptom or sign of stress urinary incontinence is confirmed with objective testing, the term *urodynamic stress incontinence* (USI), formerly known as *genuine stress incontinence* is used.

With *urge urinary incontinence* , women have difficulty postponing urination urges and generally must promptly empty their bladder on cue and without delay. If urge urinary incontinence is objectively demonstrated by cystometric evaluation, the condition is known as *detrusor overactivity* (DO), formerly known as detrusor instability (DI). When both stress and urge components are present, it is called *mixed urinary incontinence.*

Functional incontinence occurs in situations in which a woman cannot reach a toilet in time because of physical, psychological, or mentation limitations. In most instances, this group would be continent if these issues were absent.

EPIDEMIOLOGY

In western societies, most epidemiologic studies indicate a prevalence of 25 to 55 percent. This wide range is attributed to the equally wide variety of investigative methodology, population characteristics, and definitions of incontinence. Moreover, current available data are further limited by the fact that most women do not seek medical attention for this condition (Hunskaar, 2000). It is estimated that only one in four women will seek medical advice for incontinence due to embarrassment, limited access to health care, or poor screening by health care providers (Hagstad, 1985).

Among ambulatory women with urinary incontinence, the most common condition is stress incontinence, which represents 29 to 75 percent of cases. Detrusor overactivity accounts for up to 33 percent of incontinence cases, whereas the remainder is attributable to mixed forms (Hunskaar, 2000).

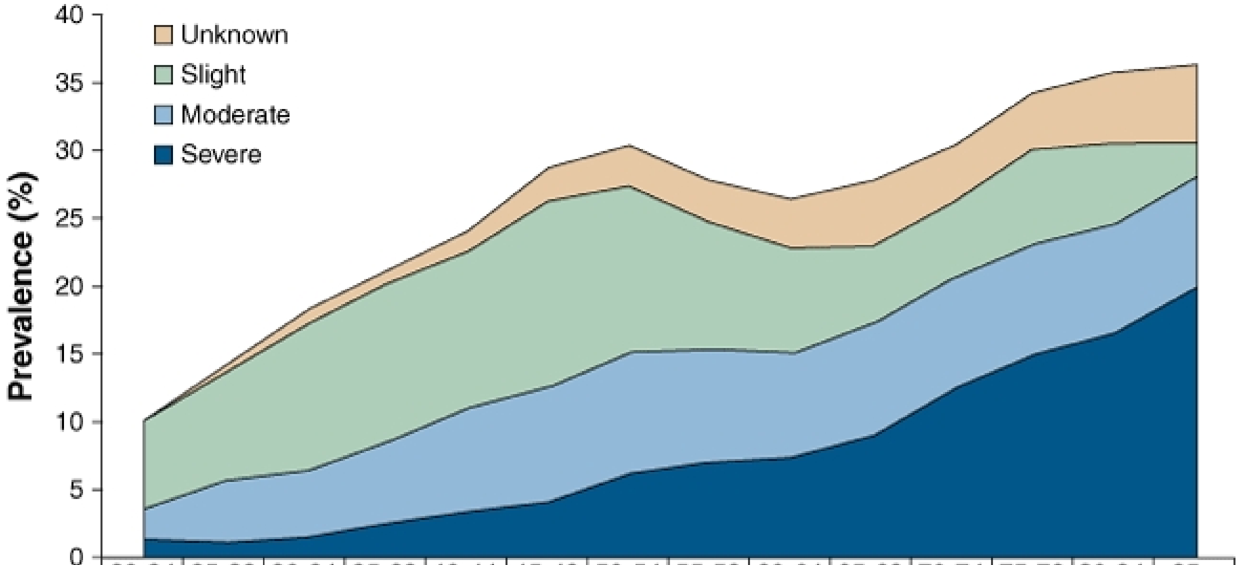
Urinary incontinence can significantly impair the quality of life, leading to disrupted social relationships, psychological distress from embarrassment and frustration, hospitalizations due to skin breakdown and urinary tract infection, and nursing home admission. An incontinent elderly woman is 2.5 times more likely to be admitted to a nursing home than a continent one (Langa, 2002).

RISKS FOR URINARY INCONTINENCE

Age

The prevalence of incontinence appears to increase gradually during young adult life (Fig. 23-1). A broad peak is noted at middle age and then steadily increases after age 65 (Hannestad, 2000).

FIGURE 23-1



	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
Unknown	0.3	0.6	1	1.1	1.6	2.4	3	3.1	3.6	4.8	4	4.2	5.2	5.7
Slight	6.3	8	10.7	11.5	11.6	13.7	12.3	9.3	7.8	5.6	5.7	7	5.9	2.6
Moderate	2.5	4.5	4.9	6	7.5	8.3	8.8	8.4	7.6	8.3	8.1	8.1	8.1	8.2
Severe	1.3	1.2	1.6	2.6	3.3	4.1	6.1	6.8	7.2	8.7	12.1	14.6	16.1	19.3

Age

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Prevalence of any (n = 6,170) and significant (n = 1,832) incontinence by age group *(From Hannestad, 2000, with permission.)*

The type of incontinence may differ by age, with some studies suggesting a higher prevalence of stress incontinence in women younger than 60 years and urge incontinence in older women (Hannestad, 2000). Not all studies confirm this finding, and the causes of these age-related trends are not clearly understood (Rortveit, 2003).

Race

Traditionally, Caucasian women are believed to have higher rates of urinary incontinence than women of other races. In contrast, urge incontinence is believed to be more prevalent among African-American women. However, these reports are not population based, and thus are not the best estimate of true racial differences. Most epidemiologic studies of urinary incontinence have been conducted in Caucasian populations. In addition, existing data on racial differences are largely based on small sample sizes (Bump, 1993). Of noted trends, it is not yet clear whether these differences are biologic, related to health care access, or affected by cultural expectations and symptom tolerance thresholds. Clearly, further study of non-Caucasian populations is needed.

Obesity

Several epidemiologic studies have shown that an increased body mass index (BMI) is a significant and independent risk factor for urinary incontinence of all types (Table 23-1). Evidence suggests that the prevalence of both urge and stress incontinence increases proportionately with BMI (Hannestad, 2003). Theoretically, the increase in intra-abdominal pressure that coincides with an increased BMI results in a proportionally higher intravesical pressure. This higher pressure overcomes urethral closing pressure and leads to incontinence (Bai, 2002). Deitel and co-workers (1988) reported a significant decline in the prevalence of stress urinary incontinence, from 61 to 11 percent, in 138 morbidly obese women following weight loss after bariatric surgery. Accordingly, as a greater proportion of our population becomes overweight and obese, we can expect to see an increase in the prevalence of urinary

incontinence in the United States (Flegal, 2002).

Table 23-1 Risk Factors for Urinary Incontinence
Age
Pregnancy
Childbirth
Menopause
Hysterectomy
Obesity
Urinary symptoms
Functional impairment
Cognitive impairment
Chronically increased abdominal pressure
Chronic cough
Constipation
Occupational risk
Smoking

Menopause

Studies have inconsistently demonstrated an increase in urinary dysfunction after a woman enters her postmenopausal years (Bump, 1998). In those with symptoms, separating hypoestrogenism effects from the effects of aging is difficult.

High-affinity estrogen receptors have been identified in the urethra, pubococcygeal muscle, and bladder trigone but are infrequently found elsewhere in the bladder (Iosif, 1981). It is believed that hypoestrogenic-related collagen changes and reductions in urethral vascularity and volume of skeletal muscle collectively may contribute to impaired urethral function via a decreased resting urethral pressure (Carlile, 1988). Moreover, estrogen deficiency with resulting urogenital atrophy is thought responsible in part for urinary sensory symptoms following menopause (Raz, 1993). Despite this current evidence that estrogen plays a role in normal urinary function, it is less clear whether estrogen therapy is useful in the treatment or prevention of incontinence (Estrogen Replacement) (Fantl, 1994, 1996).

Childbirth and Pregnancy

Many studies reveal a higher prevalence of urinary incontinence in parous women compared with nulliparous women. The effects of childbirth on incontinence may result from direct injury to pelvic muscles and connective tissue attachments. In addition, nerve damage from trauma or stretch may result in pelvic muscle dysfunction (Snooks, 1986). Specifically, a higher rate of prolonged pudendal nerve motor latency after delivery has been demonstrated in women with incontinence compared with that of asymptomatic women.

Smoking and Chronic Lung Disease

Two large epidemiologic studies have demonstrated a significant increase in the risk for urinary incontinence in women older than

60 years with chronic obstructive pulmonary disease (Brown, 1996; Diokno, 1990). Similarly, cigarette smoking is identified as an independent risk factor for urinary incontinence in several studies. In one of these studies, both current and former smokers were noted to have a two- to threefold risk of incontinence compared with nonsmokers (Bump, 1992). Theoretically, persistently increased intra-abdominal pressures are generated from a smoker's chronic cough, and collagen synthesis is diminished by the anti- estrogenic effect of smoking.

Hysterectomy

Studies have inconsistently shown that hysterectomy is a risk factor for developing urinary incontinence. Those that show an association are retrospective, lack appropriate control groups, and are often based solely on subjective data (Bump, 1998). In contrast, studies that include pre- and postoperative urodynamic testing reveal clinically insignificant changes in bladder function. Moreover, evidence does not support avoidance of clinically indicated hysterectomy nor the performance of supracervical hysterectomy as measures to prevent urinary incontinence (Vervest, 1989; Wake, 1980).

PATHOPHYSIOLOGY

Continence

The bladder is a storage organ of urine with the capacity to accommodate large increases in urine volume with minimal or no increases in intravesical pressure. The ability to maintain urine storage with convenient and socially acceptable voluntary emptying is *continence.*

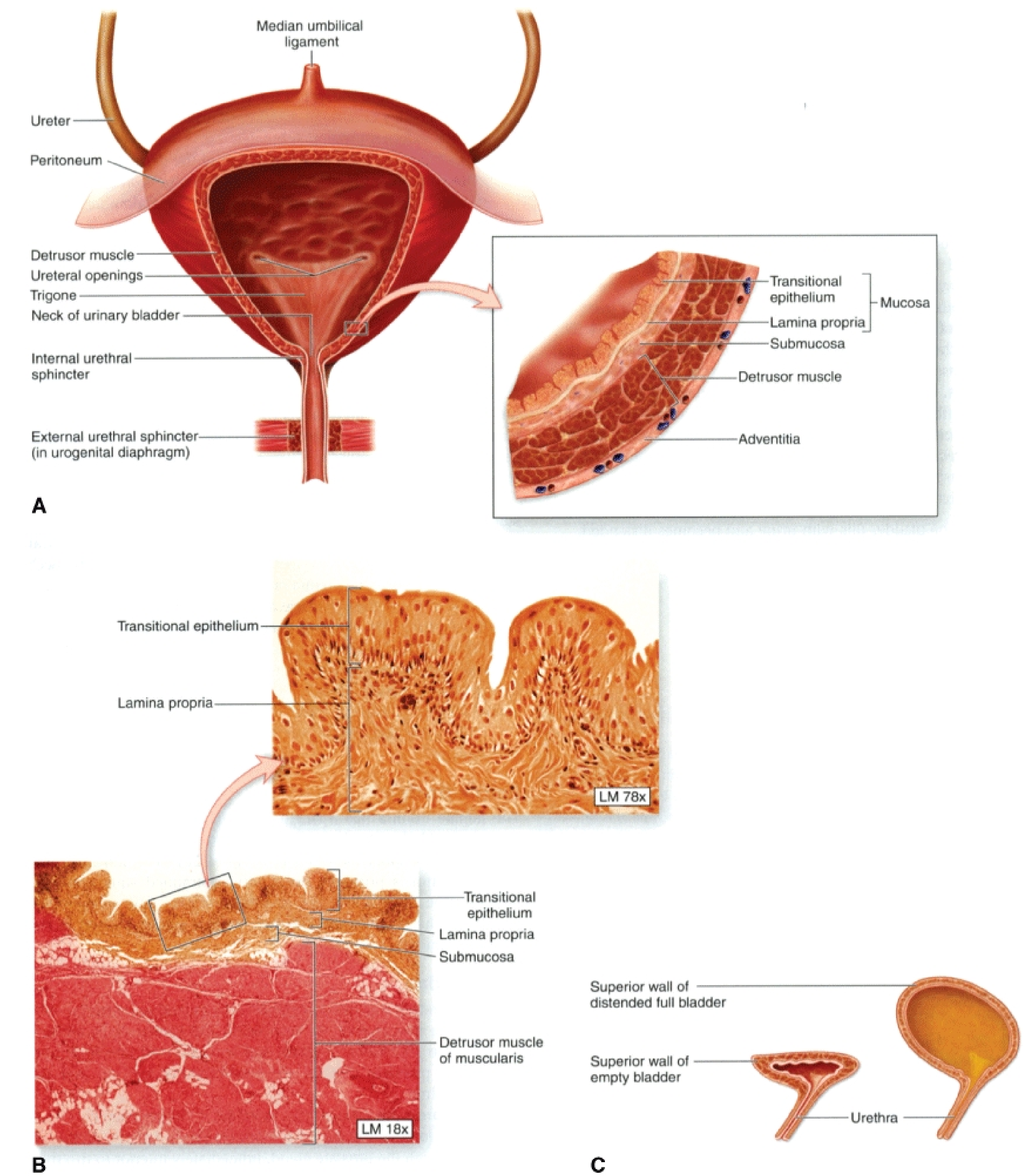
Continence requires the complex coordination of multiple components that include muscle contraction and relaxation, appropriate connective tissue support, and integrated innervation of and communication between these structures. Simplistically, during filling, urethral contraction is coordinated with bladder relaxation and urine is stored. In turn, during voiding, the urethra relaxes and the bladder contracts. These mechanisms can be challenged by uninhibited detrusor contractions, marked increases in intra-abdominal pressures, and changes to the various anatomic components of the continence mechanism.

Bladder Filling

BLADDER ANATOMY

The bladder wall is multilayered and contains mucosal, submucosal, muscular, and adventitial layers (Fig. 23-2). The bladder mucosa is comprised of a transitional cell epithelium, supported by a lamina propria. With small bladder volumes, the mucosa is thrown into convoluted folds. However, with bladder filling, it is stretched and thinned. The bladder epithelium, termed *uroepithelium* , is comprised of three distinct cell layers. The most superficial is the umbrella cell layer, and its impermeability is thought to create the primary urine-plasma barrier.

FIGURE 23-2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Bladder anatomy. **A.** Anteroposterior view of bladder anatomy. Inset: The bladder wall contains mucosal, submucosal, muscular, and adventitial layers. **B.** Photomicrograph of the bladder wall. The mucosa of an empty bladder is thrown into convoluted folds or rugae. The plexiform arrangement of muscle fibers of the detrusor muscle cause difficulty in defining its three distinct layers. **C.** Shapes and position of the bladder when empty and full. *(From McKinley, 2006, with permission.)*

In addition to its three cellular layers, the uroepithelium is covered on its cavity surface by a glycosaminoglycan (GAG) layer. This

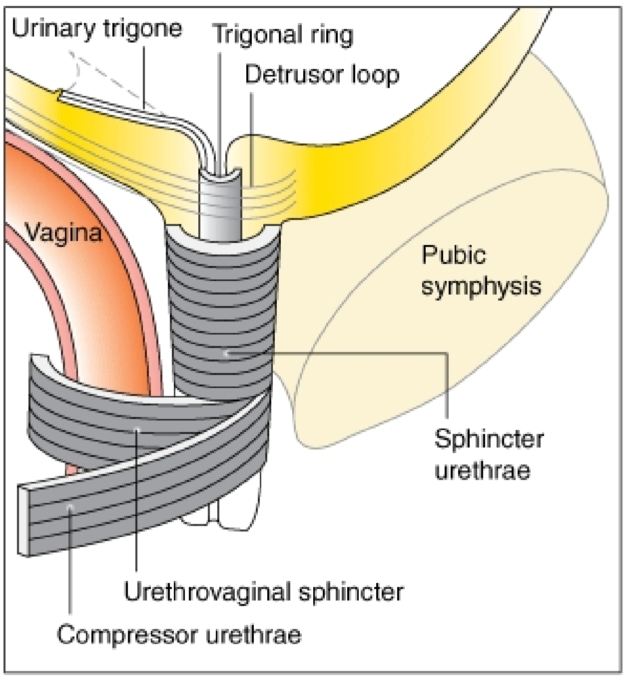
GAG layer may prohibit bacterial adherence and prevents urothelial damage by acting as a protective barrier. Specifically, theories describe that this layer of carbohydrate polymers may be defective in patients with interstitial cystitis (see Chap. 11, Interstitial Cystitis).

The muscular layer, termed the detrusor muscle, is composed of three smooth muscle layers arranged in a plexiform fashion. This unique plexiform arrangement allows for rapid multidimensional expansion during bladder filling and is a key component to the bladder's ability to accommodate large volumes of urine.

UROGENITAL SPHINCTER

As the bladder fills, synchronized contraction of the striated urogenital sphincter is integral to continence. Components of this sphincter include: (1) the *sphincter urethrae* (SU), (2) the *urethrovaginal sphincter* (UVS), and (3) the *compressor urethrae* (CU) (Fig. 23-3). The sphincter urethrae is striated muscle and wraps circumferentially around the urethra. In comparison, the UVS and CU are striated muscle bands that arch ventrally over the urethra and insert into the fibromuscular tissue of the anterior vaginal wall.

FIGURE 23-3



Striated urogenital sphincter anatomy. *(From DeLancey, 2003, with permission.)*

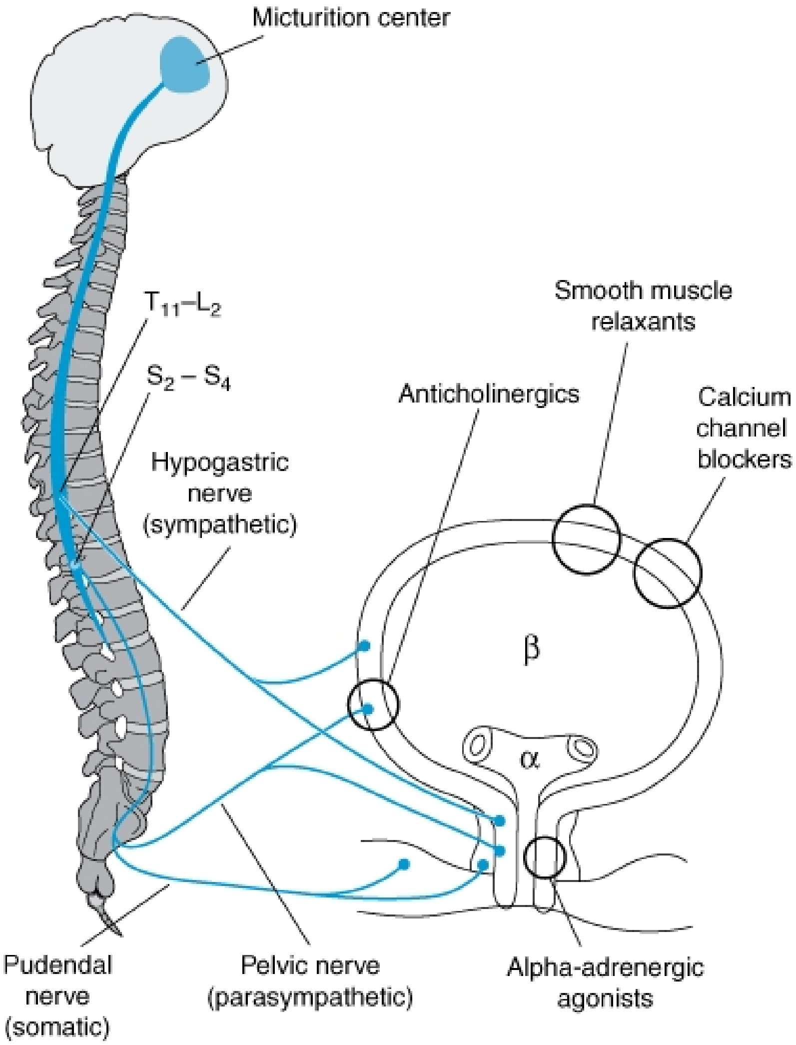
These three muscles function as a single unit and contract effectively to close the urethra. Contraction of these muscles circumferentially constricts the upper two thirds of the urethra and laterally compresses the lower one third. The sphincter urethrae is predominantly composed of slow twitch fibers and remains tonically contracted, contributing substantially to continence at rest. In contrast, the UVS and CU are comprised of fast twitch muscle fibers, which allow brisk contraction and urethra lumen closure when continence is challenged by sudden increases in intra-abdominal pressure.

INNERVATION IMPORTANT TO STORAGE

The striated urogenital sphincter muscles receive motor innervation through the pudendal nerve (Fig. 23-4). These somatic nerve fibers control the voluntary striated muscle of this sphincter. Thus, pudendal neuropathy, which may follow prolonged labor, can affect normal functioning of these muscles. Additionally, prior pelvic surgery or pelvic radiotherapy may damage nerves,

vasculature, and soft tissue. This can lead to ineffective urogenital sphincter action and contribute to incontinence.

FIGURE 23-4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

As the bladder fills, sensory afferent signals are carried through the pelvic and hypogastric nerves to the spinal cord, where they are relayed to the pontine micturition center via the lateral spinothalamic tracts and dorsal columns. Sympathetic stimulation transmitted through the hypogastric nerve maintains smooth muscleâ€"based activity of the urethral sphincter and aids in detrusor relaxation to promote urine storage. Concurrently, somatic efferent signals to the striated muscle of the pelvic floor transferred through the pudendal nerve provide voluntary urethral sphincter activity and rapid augmentation of urethral resistance in response to sudden increases in bladder pressure. As afferent signaling increases in intensity with bladder filling, a threshold of consciousness is reached, at which point a socially appropriate opportunity to void is sought. At that point, signaling from the pontine micturition center to the sacral cord travels through the reticulospinal and corticospinal tracts. Parasympathetic cholinergic stimulation of the detrusor and reflex relaxation of the striated muscle of the pelvic floor follows and urination ensues. Sites of pharmacologic agent action are shown by circles. *(From Sourander, 1990, with permission.)*

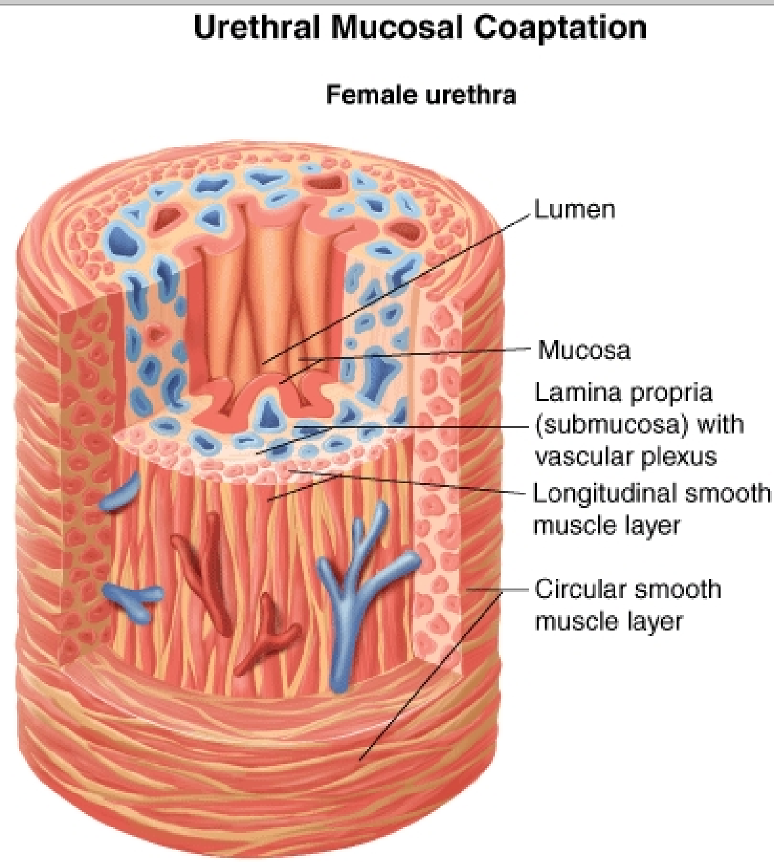
Sympathetic fibers are carried through the hypogastric nerve plexus and communicate with α- and β-receptors within the bladder and urethra (see Fig. 23-4). β-Adrenergic receptor stimulation in the bladder dome results in smooth muscle relaxation and assists with urine storage. In contrast, α_1 receptors predominate in the bladder base and urethra. Alpha-adrenergic receptors are stimulated by norepinephrine, which results in a cascade of events that preferentially leads to urethral contraction and aids urine storage and continence. These effects of alpha stimulation underlie the treatment of stress urinary incontinence with imipramine, a

tricyclic antidepressant with adrenergic agonist properties (Medications).

URETHRAL COAPTATION

One key requirement in maintaining continence is adequate urethral mucosa coaptation. As previously described, the uroepithelium is supported by a connective tissue layer, which is thrown into deep folds or plications. A rich capillary network runs within its subepithelial layer. This vascular network aids in urethral mucosal approximation, also termed *coaptation,* by acting like an inflatable cushion (Fig. 23-5). In women who are hypoestrogenic, this submucosal vasculature plexus is less prominent. In part, hormone replacement targets this diminished vascularity and enhances coaptation to improve continence.

FIGURE 23-5



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Drawing of urethral anatomy. Urethral coaptation results in part from filling of the rich subepithelial vascular plexus. The urethra contains smooth muscle layers. These are distinct from the striated urogenital sphincter (not illustrated). *(Redrawn from Craig, 1995.)*

Bladder Emptying

INNERVATION RELATED TO VOIDING

When an appropriate time for bladder emptying arises, sympathetic stimulation is reduced and parasympathetic stimulation is triggered. Specifically, neural impulses carried in the pelvic nerves stimulate acetylcholine release and lead to detrusor muscle contraction (see Fig. 23-4). Concurrent to detrusor stimulation, acetylcholine stimulates receptors in the urethra and leads to outlet relaxation for voiding.

Within the parasympathetic system, acetylcholine receptors are broadly defined as muscarinic and nicotinic. The bladder is densely supplied with muscarinic receptors. Of the muscarinic receptors, five glycoproteins designated M_1 through M_5 , have been identified.

The M_2 and M_3 receptor subtypes have been identified as mainly responsible for detrusor smooth muscle contraction. Thus, treatment with muscarinic antagonist medications blunts detrusor contraction to improve continence. Specifically, continence drugs that target only the M_3 receptor maximize drug efficacy yet minimize activation of other muscarinic receptors and drug side effects.

MUSCULAR ACTIVITY WITH VOIDING

Smooth muscle cells within the detrusor fuse with one another so that low-resistance electrical pathways exist from one muscle cell to the next. Thus, action potentials can spread quickly throughout the detrusor muscle to cause rapid contraction of the entire bladder. In addition, the plexiform arrangement of bladder detrusor fibers allows multidirectional contraction and is ideally suited for rapid concentric contraction during bladder emptying.

During voiding, all components of the striated urogenital sphincter relax. Importantly, bladder contraction and sphincter relaxation must be coordinated for effective voiding. Occasionally, tonic contraction of the detrusor may be dyssynchronous with urethral relaxation. With detrusor sphincter dyssynergia, the urethra fails to relax during detrusor contraction and retention ensues. Occasionally, women with this condition may be treated with pharmacologic agents such as muscle relaxants. These drugs purportedly relax the urethral sphincter and levator ani muscles to improve coordinated voiding.

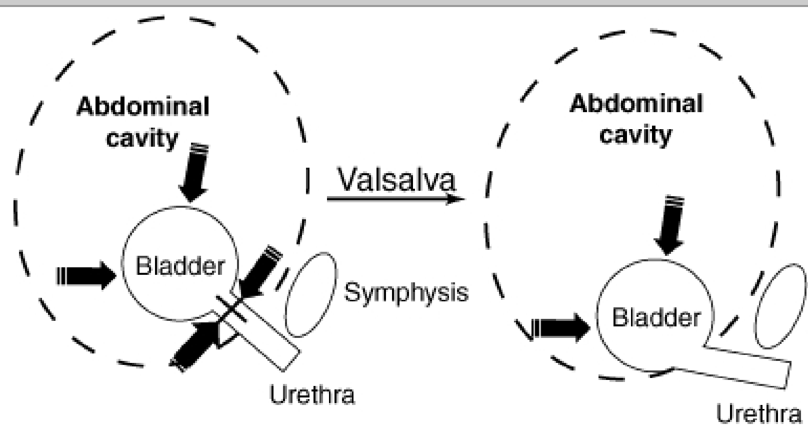
Continence Theories

Theories on continence are abundant and involve concepts relating to pressure transmission, anatomic support, and urethral integrity. These vary in the amount of supporting scientific evidence for each theory. However, currently these serve as the underpinning for current urogynecologic treatment. Precisely dissecting the mechanism behind incontinence is difficult, thus artificial separation of etiology may provide little value to the general practitioner. Thus, simplistically, continence can be conceptualized in terms of urethral support and urethral integrity.

Pressure Transmission

In an ideally supported urogenital tract, increases in intra-abdominal pressure are equally transmitted to the bladder, bladder base, and urethra. In women who are continent, increases in downward-directed pressure from cough, laugh, sneeze, and Valsalva maneuver are countered by supportive tissue tone provided by the levator ani muscle and vaginal connective tissue (Fig. 23-6). In those with a weakened supportive "backboard", however, downward forces are not countered. This leads to funneling of the urethrovesical junction, a patent urethra, and in turn, urine leakage. This mechanistic theory is the basis for surgical re-establishment of this support. Procedures such as Burch colposuspension are used to recreate this support (see Section 42-2, Burch Colposuspension).

FIGURE 23-6



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Drawing describes the pressure transmission theory. In women with normal support, increases in intra-abdominal pressure are equally distributed to contralateral sides of the bladder and urethra. In those with poor urethral support, increases in intra-abdominal pressure alter the urethrovesical angle and continence is lost.

Urethral Support

Urethral support is integral to continence. This support is derived from: (1) ligaments along the lateral aspects of the urethra, termed the pubourethral ligaments; (2) the vagina and its lateral fascial condensation; (3) the arcus tendinous fascia pelvic; and (4) levator ani muscles (see Fig. 38-11). With loss of urethral support, the urethra's ability to close against a firm supportive backboard is diminished. This results in reduced urethral closing pressures and an inability to resist increases in bladder pressure. Thus, continence is lost.

RESTORATION OF URETHRAL SUPPORT

Therapies to improve urethral support include pelvic floor muscle training (Kegel exercises) and vaginal pessary use (Pelvic Floor Strengthening Exercises). Again, urethropexy procedures such as Burch and Marshall-Marchetti-Kranz (MMK) colposuspensions attempt to re-establish this anatomic support of the urethrovesical junction and proximal urethra.

Urethral Integrity

FACTORS AFFECTING INTEGRITY

The urethra maintains continence through the combination of urethral mucosal coaptation, the viscoelastic properties of the urethral epithelium, the underlying urethral vascular plexus, and contraction of appropriate surrounding musculature (see Fig. 23-5). Defects in any of these components may lead to urine leakage.

For example, prior surgery in the retropubic space may cause denervation and scarring of the urethra and its supporting tissue. These effects subsequently prevent urethral closure and lead to incontinence. This resulting urethral state is termed *intrinsic sphincteric defect* (ISD), and colloquially is referred to as a "lead pipe" urethra. With ISD, denervation and/or devascularization of the urethra are common underlying findings. Specific causes are varied and include prior pelvic reconstructive surgeries, prior pelvic radiotherapy, hypoestrogenism, diabetic neuropathy, and neuronal degenerative diseases. In women with atrophic lower genital tracts, vascular changes within the plexus surrounding the urethra lead to poor coaptation and greater risks of incontinence. Accordingly, estrogen replacement therapy targets this vascular system and often leads to greater mucosal coaptation and improved continence.

Trauma associated with childbirth may alter lower urinary tract innervation and may lead to immediate and potentially persistent incontinence. In these situations, nerve dysfunction following birth trauma to the urethra leads to defective sphincter function. In addition, childbirth also commonly injures fascial support to the urethra. This clinical example highlights the intimate relationship between urethral support and urethral integrity.

RESTORATION OF URETHRAL INTEGRITY

Treatment directed at restoring urethral integrity includes transurethral injection of bulking agents, surgical sling procedures, and pelvic floor muscle strengthening. Bulking agents such as collagen are placed below the urethral muscularis at the level of the urethrovesical junction to elevate the epithelium and promote coaptation. Alternatively, the partially obstructive nature of pubovaginal sling procedures enhances urethral integrity. Lastly, because the urethra exits through the urogenital hiatus, conditioning of the levator ani muscles with pelvic floor muscle training can bolster urethral integrity. These muscles can be contracted around the urethra when continence is challenged by sudden increases in intra-abdominal pressures.

DIAGNOSIS

History

SYMPTOM CLUSTERING

To methodically quantify symptoms for research purposes and compare outcomes between different treatments for incontinence,

investigators have created a variety of validated patient questionnaires to evaluate treatment efficacy (Kelleher, 1997; Patrick 1999; Wagner 1996). Many of these tools are lengthy and may be impractical for general clinical practice. More simply, assessment of incontinence may begin with a description of urinary symptoms. This inventory may be collected through direct conversation, but more commonly begins with completion of a patient questionnaire as shown in Table 23-2.

Table 23-2 Review of Systems for Women with Urinary Incontinence

Leak with stress	Y/N
Leak with urge	Y/N
Leak with position changes	Y/N
Leak with exercise	Y/N
Leak with intercourse/orgasm	Y/N
Unconscious leakage	Y/N
Duration of symptoms______wk______mo______yr	
Leaks per______day______wk______mo	
Pads per day______Type of pads______	
Voids daytime:_________	
Voids nighttime:__________	
Constipation	Y/N
Self Rx with__________________________________	
BMs_________/day_________/week	
Anal incontinence	Y/N
Duration__________mo__________yr	
Flatus__________/wk__________/mo	
Liquid__________/wk__________/mo	
Stool__________/wk__________/mo	
Digital decompression of bowel	Y/N
Digital decompression of bladder	Y/N
Postvoid dribble	Y/N
Feeling of incomplete emptying	Y/N
Recurrent UTI___________/yr	

Void with Valsalva	Y/N
Urine stream: strong/normal/weak	
Childhood enuresis	Y/N
Frequency	Y/N
Urgency	Y/N
Dysuria	Y/N
Hematuria	Y/N
Back pain	Y/N
Pelvic pressure/Bulge	Y/N
Dyspareunia	Y/N
Rectal bleeding	Y/N
Does heavy lifting	Y/N
Interfers w/lifestyle or quality of life	Y/N

During inquiry, the number of voids and pads used per day, type of pad, frequency of pad changing, and the degree of pad saturation are important considerations. Although these specifics alone may not establish the exact type of incontinence, they do provide information regarding symptom severity and its effects on patient activities. Obviously, if a woman's symptoms do not diminish her quality of life, then simple observation is reasonable. Conversely, those with disruptive symptoms warrant further evaluation.

Specific to incontinence, information that describes the circumstances in which leakage occurs and specific maneuvers that incite or provoke leakage should be sought. With stress urinary incontinence (SUI), provokers may include increases in intra-abdominal pressure such as coughing, sneezing, Valsalva maneuver, or thrusting during intercourse (Table 23-3). Alternatively, women with urge incontinence may describe a loss of urine after sensations of urgency, which typically cannot be suppressed.

Table 23-3 Symptom Comparison of Women with Stress or Urge Incontinence

Symptom	**Urge Incontinence**	**Stress Incontinence**
Urgency	Yes	No
Frequency with urgency	Yes	No
Urine leakage with increased intra-abdominal pressures	No	Yes
Amount of urinary leakage with each incontinence episode	Large (if present)	Small
Ability to reach the toilet in time following an urge to void	Often no	Yes
Waking to void at night	Usually	Seldom

Overflow incontinence was a term used in the past to refer to women who had an inability to empty their bladder and had episodes

of incontinence associated with urgency. Currently, however, this is considered by most to reflect another presentation of urge urinary incontinence. These women often note a sudden large loss of urine that is preceded by an inability to empty their bladder.

During questioning, symptoms typically cluster into those most frequently seen with SUI or with urge urinary incontinence. Alternatively, a significant overlap of complaints may reflect co-existent SUI and urge urinary incontinence, that is, mixed urinary incontinence. For these reasons, pattern identification is helpful and may direct diagnostic testing and guide initial empiric therapy.

VOIDING DIARY

Typically, patients may not have an entirely accurate recollection of their own voiding habits. Accordingly, to obtain a thorough record, a woman should complete a urinary diary (Fig. 23-7). With this, women are instructed to record for 3 days the volumes of each oral fluid intake, volumes of urine with each void, episodes of urinary leakage, and provokers of incontinence episodes. During each 24-hour period, women should also record times of sleep and awakening. This enables an accurate description of voluntary nocturnal voiding patterns as well as enuresis. Although 5 to 7 days of documentation is desirable, 3 days will suffice in determining the general trend of incontinence. Furthermore, realistically, most are typically not compliant for more than 3 days.

FIGURE 23-7

Bladder Diary

Please record the time and amount of your oral intake, urine output, urine leakage, and pad changes FOR 3 DAYS

Time	Oral Intake	Voided Urine	Urine Leakage or Pad Change

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Example of a urinary diary.

The historical information gained from a voiding/urinary diary is a valuable diagnostic tool. Moreover, this method of quantifying incontinence can also be used again later to provide an assessment of treatment efficacy.

URINARY SYMPTOMS

Urinary Frequency

Most women void eight times per day or less. Without a history that reflects increased fluid intake, increased voiding may indicate urge incontinence, urinary tract infection, calculi, or urethral pathology, and should prompt additional evaluation. In addition, urinary frequency is commonly associated with interstitial cystitis (IC). In women with IC, the number of voids may commonly exceed 20 per day. In women with urge incontinence or in those with systemic fluid management disorders such as congestive heart failure, nocturia may be noted. In the latter case, treatment of the underlying condition frequently leads to symptom improvement or cure.

Urinary Retention

It is important to determine if the patient adequately empties her bladder. Often incomplete emptying can result in incontinence associated with either stress or urgency. The term overflow incontinence is no longer used.

Other Urinary Symptoms

The volume of urine lost with each episode may also provide diagnostic clues. Large volumes are typically lost following the spontaneous detrusor contractions associated with urge urinary incontinence and may often involve loss of the entire bladder volume. In contrast, women with SUI usually describe smaller volumes lost. Moreover, these women often are able to contract the levator ani muscles to temporarily stop their urine stream.

Postvoid dribbling is classically associated with urethral diverticulum, which may often be mistaken for urinary incontinence (see Chap. 26, Patient Signs and Symptoms). Hematuria, although a common sign of UTI, may also indicate underlying malignancy and can cause irritative voiding symptoms.

The onset of symptoms may also provide information regarding etiology and treatment. For example, onset of symptoms with the menopause may suggest that a hypoestrogenic state underlies incontinence. These patients may benefit from estrogen replacement. In contrast, symptoms after hysterectomy or childbirth may reflect changes in tissue support or innervation.

PAST MEDICAL HISTORY

In addition to specific details describing urinary symptoms, other medical factors may be associated with incontinence. Obstetric trauma may be associated with damage to pelvic floor support, which may lead to SUI. For this reason, information describing a prolonged labor, operative vaginal delivery, macrosomia, postpartum catheterization for urinary retention, and increased parity may be valuable. Prior radiation therapy for malignancy may lead to irritative voiding symptoms or intrinsic sphincteric deficiency, which predisposes to SUI. Finally, a detailed medication inventory should be collected. Pertinent drugs may include estrogen, α-adrenergic agonists, and diuretics (Table 23-4).

Table 23-4 Medications that May Contribute to Incontinence

Medication	Examples	Mechanism	Effect
Alcohol	Beer, wine, hard liquor	Diuretic effect, sedation, immobility	Polyuria, frequency
α-adrenergic agonists	Decongestants, diet pills	IUS contraction	Urinary retention
α-adrenergic blockers	Prazosin, terazosin, doxazosin	IUS relaxation	Urinary leakage
Anticholinergic agents		Inhibit bladder contraction, sedation, fecal impaction	Urinary retention and/or functional incontinence
Antihistamines	Diphenhydramine, scopolamine, dimenhydrinate		
Antipsychotics	Thioridazine, chlorpromazine, haloperidol		
Antiparkinsonians	Trihexyphenidyl, benztropine mesylate		
Miscellaneous	Dicyclomine, disopyramide		
Skeletal muscle relaxants	Orphenadrine, cyclobenzaprine		
Tricyclic antidepressants	Amitriptyline, imipramine, nortriptyline, doxepin		
Angiotensin-converting enzyme (ACE) inhibitors	Enalapril, captopril, lisinopril, losartan	Chronic cough	Urinary leakage

Calcium-channel blockers	Nifedipine, nicardipine, isradipine, felodipine	Relaxes bladder, fluid retention	Urinary retention, nocturnal diuresis
Cyclooxygenase-2 selective NSAIDs	Celecoxib	Fluid retention	Nocturnal diuresis
Diuretics	Caffeine, HCTZ, furosemide, bumetanide, acetazolamide, spironolactone	Increases urinary frequency, urgency	Polyuria
Narcotic analgesics	Opiates	Relaxes bladder, fecal impaction, sedation	Urinary retention, and/or functional incontinence
Thiazolidinediones	Rosiglitazone, pioglitazone, troglitazone	Fluid retention	Nocturnal diuresis

HCTZ = hydrochlorothiazide; IUS = internal urethral sphincter; NSAID = nonsteroidal anti-inflammatory drug.

Physical Examination

GENERAL INSPECTION AND NEUROLOGIC EVALUATION

Initially, the perineum is inspected for evidence of atrophy, which may be noted throughout the lower genital tract. In addition, suburethral bulging may indicate a urethral diverticulum and should be excluded during inspection (see Chap. 26, Patient Signs and Symptoms).

A thorough physical examination for a woman with incontinence should also include a detailed neurologic evaluation of the perineum. Because neurologic responses may be altered in an anxious patient who is in a vulnerable setting, signs elicited during examination may not signify true pathology and should be interpreted with caution. Neurologic evaluation begins with attempting to elicit a *bulbocavernosus reflex.* During this test, one labium majora is stroked with a cotton swab. Normally, both labia equally contract bilaterally. The afferent limb of this reflex is the clitoral branch of the pudendal nerve, whereas its efferent limb is conducted through the inferior hemorrhoidal branch of the pudendal nerve. This reflex is integrated at the S2 to S4 spinal cord level (Wester, 2003). Thus, absence of this reflex may reflect central or peripheral neurologic deficits. Secondly, a normal circumferential anal sphincter contraction, colloquially called an "anal wink", should follow cotton swab brushing of the perianal skin. External urethral sphincter activity requires at least a degree of intact S2 to S4 innervation, and this *anocutaneous reflex* is mediated by the same spinal neurologic level. Thus, an absent wink may indicate neurologic deficits in this neurologic distribution.

PELVIC SUPPORT ASSESSMENT

Pelvic Organ Prolapse Evaluation

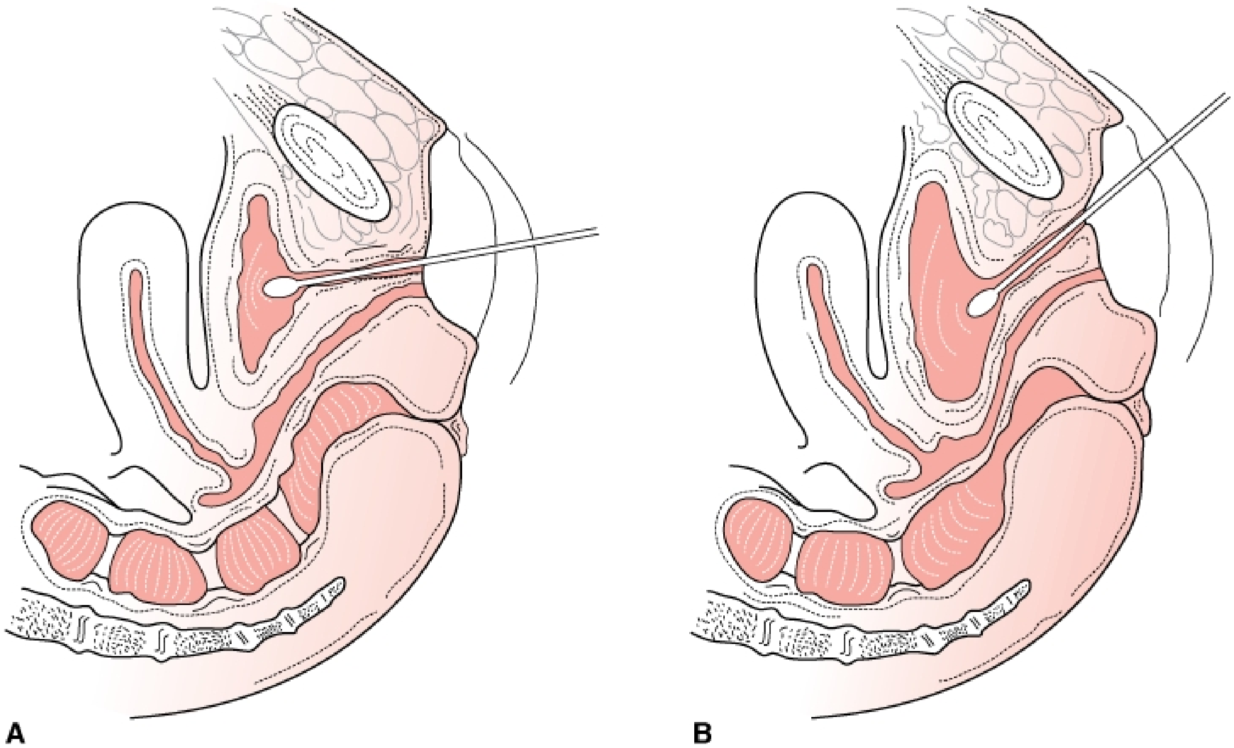
Poor urethral support commonly accompanies pelvic organ prolapse (POP). For example, women with significant prolapse are often unable to completely empty their bladder due to urethral kinking and obstruction. These women frequently must digitally elevate or reduce their prolapse to allow emptying. Thus, an external evaluation for POP, as described in Chapter 24, Physical Examination, is indicated for all women with urinary incontinence. Following this evaluation for vaginal compartment defects, pelvic muscle strength evaluation should also be performed. Women with mild to moderate urinary incontinence often respond well to pelvic floor therapy and under these circumstances, a trial of this therapy is warranted and often curative.

Q-Tip Test

If a urethra is poorly supported, it may display hypermobility during increases in intra-abdominal pressures. To assess mobility, a clinician places the soft end of a cotton swab into the urethra to the urethrovesical junction. Failure to insert the swab to this depth typically leads to errors in assessment of urethrovesical junction support. Termed the *Q-tip test,* this evaluation may be uncomfortable and application of intraurethral analgesia may prove helpful. Commonly, 1 percent lidocaine jelly is placed on the cotton swab prior to insertion. Following placement, Valsalva maneuver is prompted, and the swab angle excursion at rest and with

Valsalva maneuver is measured with a goniometer or standard protractor (Fig. 23-8). An angle excursion at rest or with Valsalva maneuver greater than 30 degrees above the horizontal indicates urethral hypermobility, and may help direct planning of surgical treatment for stress incontinence.

FIGURE 23-8



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Drawing depicting Q-tip test in a patient with urethral hypermobility. **A.** Angle of the Q-tip at rest. **B.** Angle of the Q-tip with Valsalva maneuver or other increases in intra-abdominal pressure. The urethrovesical junction descends, causing upward deflection of the Q-tip. *(From Tarnay, 2007, with permission.)*

BIMANUAL AND RECTOVAGINAL EXAMINATION

In general, these portions of the pelvic examination provide fewer diagnostic clues to underlying causes of incontinence. However, bimanual examination may reveal an enlarged pelvic mass or a uterus enlarged by leiomyomas or adenomyosis. These may prompt incontinence through increased external pressure transmitted to the bladder. In addition, stool impaction is common in nursing home patients and may lead to bladder urgency and subsequent urinary incontinence.

Diagnostic Testing

URINALYSIS AND CULTURE

In all women with urinary incontinence, infection or urinary tract pathology must be excluded. Urinalysis and urine culture is sent at an initial visit. Infection is treated as described in Table 3-24, and persistent symptoms should prompt additional evaluation.

POSTVOID RESIDUAL

This volume is routinely measured during incontinence evaluation. After a woman voids, the postvoid residual (PVR) may be measured with a hand-held sonographic scanner or by transurethral catheterization. If using a hand-held scanner, care must be taken in women with an enlarged leiomyomatous uterus, as this may falsely record a large PVR. In these instances, or if a scanner is not available, transurethral catheterization may be used to confirm residual bladder volume.

A large postvoid residual may often reflect one of several problems, including recurrent infection, urethral obstruction from a pelvic mass, or neurologic deficits. In contrast, a normally small PVR is often found in those with stress urinary incontinence.

Postoperative Postvoid Residual

After anti-incontinence surgery, PVR measurement is a helpful indicator of a patient's ability to completely empty her bladder. This evaluation may be completed with a passive or an active voiding trial.

With a *passive voiding trial* , a urinary catheter is removed, and the PVR is measured by scanner or by transurethral catheterization after each voluntary void on two occasions. A voided volume of at least 300 mL and PVR less than 100 mL is desirable. However, adequate bladder emptying is assumed if the PVR is less than one third of the voided volume. If a patient does not meet these criteria, or if she is unable to void within 4 to 6 hours of discontinuing the urinary catheter, then a catheter is replaced and the test is repeated a day or more later.

During an *active voiding trial* , the bladder is actively filled with a set volume, and following patient voiding, residual bladder urine volumes are calculated. Initially, the bladder is completely emptied by catheterization. It may be helpful during catheterization for a woman to stand upright to clear the most dependent portions of her bladder. Sterile water is infused under gravity into the bladder through the same catheter until approximately 300 mL is used or until a subjective maximum capacity is reached. The patient is then asked to void spontaneously into a urine collection device. The difference between volume infused and volume retrieved is recorded as the postvoid residual (PVR). A residual of less than 100 mL or one third of the instilled volume, if less than 300 mL is infused, indicates adequate bladder emptying.

CYSTOMETRICS

Surgical correction of incontinence is invasive and not without risk. Moreover, the "bladder is an unreliable witness" and historical information may not always accurately indicate the true underlying type of incontinence (Blaivas, 1996). Thus, if initial conservative management is unsuccessful or surgical treatment is anticipated, then objective assessment should be pursued. In addition, if symptoms and physical findings are incongruous, then an objective urodynamic study (UDS), using cystometric evaluation, may also be indicated. For example, in women with mixed urinary incontinence, who have both symptoms of stress and urge urinary incontinence, UDS may reveal that only the urge component is responsible for their incontinence. Most of these women are treated with behavioral, physical, and/or pharmacologic therapy initially. Thus, if urge incontinence is identified by UDS, unnecessary surgery can be avoided. Additionally, surgical therapy may be modified if UDS reveals parameters consistent with intrinsic sphincteric defect.

Despite these indications, UDS remains controversial. Leakage noted during testing is not always clinically relevant. In contrast, testing may be uninformative if the original offending maneuver or situation that led to incontinence cannot be reproduced during evaluation. Moreover, objective confirmation of the diagnosis is not always necessary, since empiric therapy in women with urge-predominant symptoms is reasonable.

Simple Cystometrics

Objective measurements of bladder function are combined in a battery of tests termed *cystometrics.* Cystometrics may be *simple* or *multichannel* and differ in their sensitivity.

Simple cystometrics allows determination of stress incontinence and detrusor overactivity, as well as measurement of first sensation, desire to void, and bladder capacity. This procedure is easily performed with sterile water, a 60-mL catheter-tipped syringe, and urinary catheter, either Foley or Robnell. The urethra is sterilely prepared, the catheter is inserted, and the bladder is drained. A 60-mL syringe with its plunger removed is attached to the catheter and is filled with sterile water. Water is added in increments until a woman feels: (1) a sensation of bladder filling, (2) an urge to void, and (3) her bladder maximum capacity. Water volumes are noted at each three of these points. Changes in the fluid meniscus within the syringe are monitored. Any meniscus elevation indicates bladder contraction and establishes a diagnosis of detrusor overactivity. Once bladder capacity is reached, the catheter is removed, and the woman is asked to perform a Valsalva maneuver or cough while standing. Leakage indicates SUI.

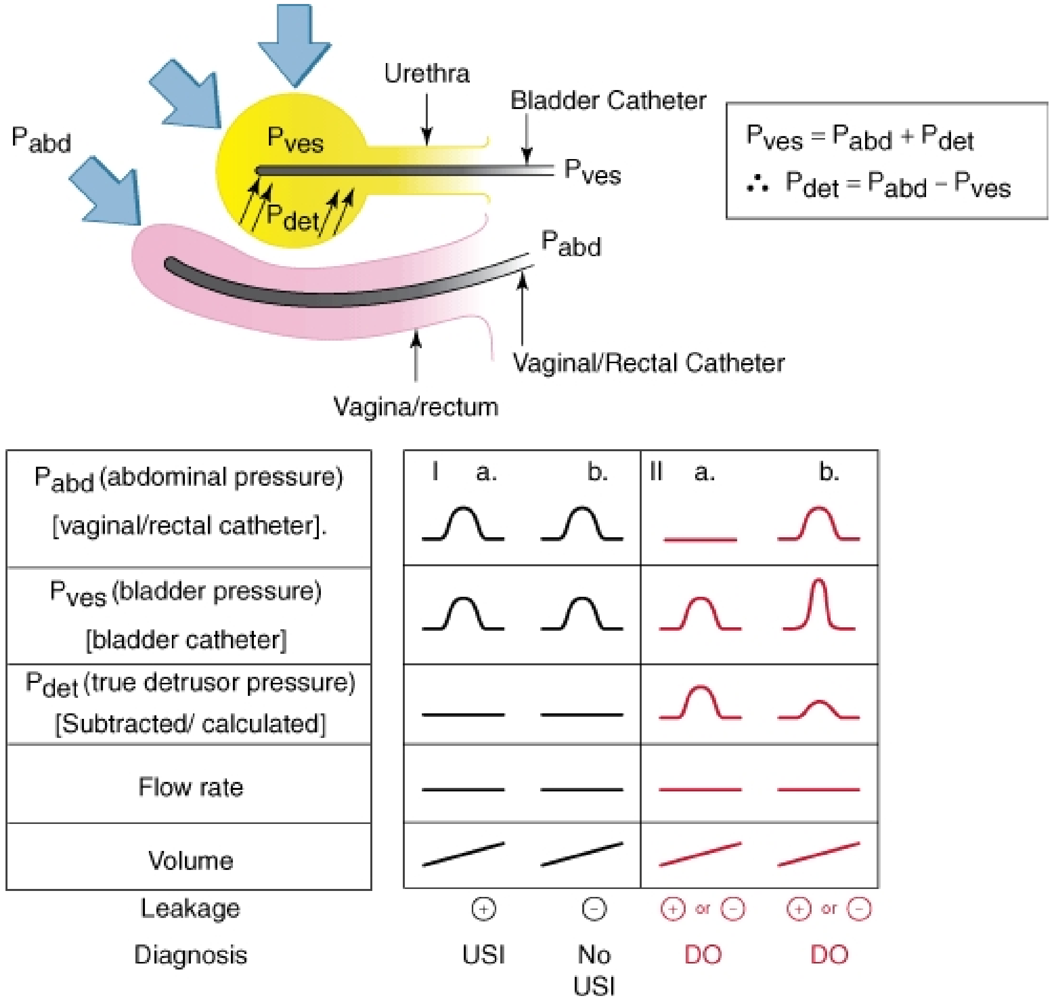
Advantageously, simple cystometrics are easy to perform, require inexpensive equipment, and can typically be completed by most gynecologists. One limitation of simple cystometric testing, however, is its inability to reflect changes found with intrinsic sphincteric deficiency (ISD).

Multichannel Cystometrics

As noted, simple cystometric testing does not identify ISD. This determination is important, since this diagnosis may potentially preclude certain surgical options. Additionally, multichannel cystometrics provides more information on other physiologic parameters of the bladder, not afforded by simple cystometrics.

Multichannel cystometrics is more commonly performed by urogynecologists or urologists due to limited equipment availability and increased costs. Testing can be performed with a woman standing or seated upright in a specialized urodynamics evaluation chair. During testing, two catheters are used. One is placed into the bladder and the other into either the vagina or rectum. The vagina is preferred unless advanced prolapse is evident because stool in the rectal vault may obstruct catheter sensors and lead to inaccurate readings. Additionally, vaginal placement for most women is more comfortable. From each of these two catheters, distinct pressure readings are obtained or calculated and include: (1) intra-abdominal pressure, (2) vesicular pressure, (3) calculated detrusor pressure, (4) bladder volume, and (5) saline infusion flow rate. From these catheter readings, information regarding bladder, intra-abdominal, and detrusor pressures can be obtained. As shown Figure 23-9, differentiation between the different forms of incontinence can be determined.

FIGURE 23-9



Interpretation of multichannel urodynamic evaluation: cystometrogram. A catheter is placed in the bladder to determine the pressure generated within it (P_{ves}). The pressure in the bladder is produced from a combination of the pressure from the abdominal cavity and the pressure generated by the detrusor muscle of the bladder.Bladder pressure (P_{ves}) = Pressure in abdominal cavity (P_{abd}) + Detrusor pressure (P_{det}). A second catheter is placed in the vagina (or rectum if advanced stage prolapse is present) to determine the pressure in the abdominal cavity (P_{abd}). As room temperature water is instilled into the bladder, the patient is asked to cough every 50 mL and the external urethral meatus is observed for leakage of urine around the catheter. The volume at first desire to void and the bladder capacity is recorded. Additionally, the detrusor pressure (P_{det}) channel is observed for positive deflections to determine if there is detrusor activity during testing. The detrusor pressure (P_{det}) cannot be measured directly by any of the catheters. However, from the first equation, we can calculate the detrusor pressure (P_{det}) by subtracting the bladder pressure from the abdominal pressure (P_{abd}):

Detrusor pressure (P_{det}) = Bladder pressure (P_{ves}) â€“ Pressure in abdominal cavity (P_{abd})

I. Urodynamic Stress Incontinence (USI)

Urodynamic stress incontinence is diagnosed when urethral leakage is seen with increased abdominal pressure, in the ABSENCE of detrusor pressure.

a. +USI (Column 1): Abdominal pressure is generated with Valsalva maneuver or cough. This pressure is transmitted to the bladder and a bladder pressure (P_{ves}) is noted. The calculated detrusor pressure is zero. Leakage is observed and diagnosis of USI is assigned.

b. No USI (Column 2): Abdominal pressure is generated with Valsalva maneuver or cough. This pressure is transmitted to the bladder and a bladder pressure (P_{ves}) is noted. The calculated detrusor pressure is zero. Leakage is NOT observed. The patient is NOT diagnosed as having

USI.

II. Detrusor Overactivity (DO)

Detrusor overactivity is diagnosed when the patient has involuntary detrusor contractions during testing with or without leakage.

a. +DO (Column 3): Although no abdominal pressure is observed, a vesicular pressure is noted. A calculated detrusor pressure is recorded and noted to be present. A diagnosis of DO is made regardless of whether leakage is seen or not.

b. +DO (Column 4): In this example, an abdominal pressure is observed as well as a vesicular pressure is noted. Using only the Pabd and the Pves channels, it is difficult to tell whether or not the detrusor muscle contributed to the pressure generated in the bladder. On subtraction, a calculated detrusor pressure is recorded. Thus, a diagnosis of DO is made, again regardless of whether leakage is seen or not.

In addition to these channels, occasionally a channel to detect electromyographic activity is used. Flow rate = rate of fluid infusion (usually 100 mL/min); P_{abd} = pressure in abdominal cavity; P_{det} = detrusor pressure (calculated); P_{ves} = bladder pressure; Vol = volume of fluid instilled in the bladder.

Uroflowmetry

Initially, women are asked to empty their bladder into a commode connected to a flowmeter (uroflow-metry). After a maximal flow rate is recorded, the patient is catheterized to measure a postvoid residual as well as to ensure an empty bladder prior to further testing. This test provides information on a woman's ability to empty her bladder. It can identify women with urinary retention and other types of voiding dysfunction.

Cystometrography

Following uroflowmetry, cystometrography is performed to determine whether a woman has urodynamic evidence of SUI or detrusor overactivity (DO). Moreover, this test provides information on bladder threshold volumes at which a woman senses bladder capacity. Delayed sensation or a sensation of bladder fullness only with large capacities may indicate neuropathy. Conversely, extreme bladder sensitivity may suggest sensory disorders such as interstitial cystitis.

For the cystometrogram, a 6F microtransducer catheter (Mikro-tip, Millar Instruments Inc., Houston, TX) is inserted transurethrally into the bladder, and a second catheter is inserted into the vagina. For women with advanced prolapse who may not be able to accommodate or retain the second catheter in their vagina, the second catheter is placed in the rectum. The bladder is filled with room temperature 0.9-percent normal saline at a rate of 100 mL/min using a cystometric pump. During filling, a woman is asked to cough at each 50-mL interval. Additionally during filling, the volumes at which a first desire to void and maximal bladder capacity are noted.

From pressure readings, DO and/or urodynamic SUI may be identified. Once 200 mL of saline has been instilled, an abdominal *leak point pressure* is measured. The patient is asked to perform a Valsalva maneuver, the pressure generated by the effort is measured, and evidence of urine leakage is sought. If leakage is seen when a pressure of less than 60 cm H_2O is generated, then criteria have been met for a diagnosis of intrinsic sphincteric deficiency.

At our institution, abdominal leak point pressures are measured at a bladder volume of 200 mL, using the true zero of intravesical pressure as the baseline. However, the volume at which this test is performed varies from institution to institution, with some choosing to use bladder capacity and others choosing to use 150 mL as the testing volume.

Pressure Flowmetry

This evaluation usually follows cystometrography and is similar to the uroflowmetry conducted at the beginning of urodynamic testing. A woman is asked to void into a beaker that rests on a calibrated weighted sensor. Maximum flow rate and postvoid residual are once again recorded. However, during voiding, a woman now has a microtip transducer catheter in her bladder, which provides additional information regarding detrusor pressure at maximum flow. This is particularly useful in women who may have incomplete bladder emptying. As noted earlier, in women with urinary retention, the offending source may be obstruction or poor detrusor contractility.

Urethral Pressure Profile

The final part of UDS testing is the urethral pressure profile. At our institution, we usually perform this test with a volume of 200

mL instilled in the bladder. However, again, this volume is often institution dependent. With a catheter transducer directed to a nine o'clock position within the bladder, the microtip dual-sensor catheter is pulled through the urethra with the aid of an automated puller arm (UPP Puller, Laborie Medical Technologies Corp., Williston, VT) at a speed of 1 mm/s. Maximum urethral closure pressure (MUCP) is determined by averaging three profiles. The *functional urethral length* and the *area of continence zone* are also obtained. This test provides valuable information on the intrinsic properties of the urethra and aids in the diagnosis of ISD. A diagnosis of ISD is made if the MUCP is 20 cm H_2O or less.

TREATMENT

Conservative/Nonsurgical

PELVIC FLOOR STRENGTHENING EXERCISES

Conservative management is a reasonable initial approach to most patients with urinary incontinence. The rationale behind conservative management is to strengthen the pelvic floor and provide a supportive backboard against which the urethra may close. Options include active pelvic floor exercises and passive electrical pelvic floor muscle stimulation. For both SUI and urge incontinence these fundamentals prove valuable. With SUI, pelvic floor strengthening is an attempt to compensate for anatomic defects. For urge incontinence, it improves pelvic floor muscle contraction to provide temporary continence during waves of bladder detrusor contraction.

Pelvic Floor Muscle Training (PFMT)

In women who have mild to moderate symptoms of urinary incontinence, pelvic floor muscle training (PFMT) may allow improvement if not cure. Also known as *Kegel exercises,* PFMT entails voluntary contraction of the levator ani muscles. As with any muscle building, exercise sets should be performed numerous times during the day, with some reporting up to 50 or 60 times each day.

Specific details in performance of these exercises are subject to clinician preference and clinical setting. In one variation of these exercises, isotonic contraction is used, and a woman is asked to squeeze and hold contracted levator ani muscles. Women, however, often have difficulty isolating these muscles. Frequently, women will erroneously contract their abdominal wall muscles rather than the levators during these exercises. To help localize the correct group, a woman may be instructed to identify the muscles that are tightened when snug pants are pulled up and over her hips. Moreover, in an office setting, a clinician can determine if the levator ani group is contracted by placing two fingers in the vagina while Kegel exercises are practiced.

Alternatively, a second variation of PFMT uses a method of rapid contraction and relaxation of the levators. This approach may prove advantageous if waves of urinary urgency strike. Of note, there is a misconception about the value of stopping urination midstream. Women should be counseled that this practice often worsens voiding dysfunction.

To augment efficacy of these exercises, weighted vaginal cones or obturators may be placed into the vagina during Kegel exercises. These provide resistance against which pelvic floor muscles can work.

Electrical Stimulation

As an alternative to active pelvic floor contraction, a vaginal probe may be used to deliver low-frequency electrical stimulation to the levator ani muscles. Although the mechanism is unclear, electrical stimulation may be used to improve either SUI or urge incontinence (Indrekvam, 2001; Wang 2004). With urge incontinence, traditionally a low frequency is applied, whereas higher frequencies are used for SUI. Electrical stimulation may be used alone or more commonly in combination with PFMT.

Biofeedback Therapy

Many behavioral techniques, often considered together as *biofeedback therapy,* measure physiologic signals such as muscle tension and then display them to a patient in real time. In general, visual, auditory, and/or verbal feedback cues are directed to the patient during these therapy sessions. These cues provide immediate performance evaluation to a patient. Specifically, during biofeedback for PFMT, a sterile vaginal probe that measures pressure changes within the vagina during levator ani muscle contraction is typically used. Readings reflect an estimate of muscle contraction strength. Treatment sessions are individualized, dictated by the

underlying dysfunction, and modified based on response to therapy. In many cases, reinforcing sessions at various subsequent intervals may also prove advantageous.

DIETARY

Different food groups that may have high acidity or caffeine content may lead to greater urinary frequency and urgency. Dallosso and colleagues (2003) found consumption of carbonated drinks to be associated with development of urge incontinence symptoms. Accordingly, elimination of these dietary irritants may prove beneficial for these women. In addition, certain supplements such as calcium glycerophosphate (Prelief, AkPharma, Pleasantville, NJ), when added to the diet have been shown to decrease urgency and frequency symptoms (Bologna, 2001). This is a phosphate-based product and is thought to buffer urine acidity.

SCHEDULED VOIDING

For women with urge urinary incontinence, voiding urges may occur as frequently as every 10 to 15 minutes. Initial goals are to extend actual voidings to half-hour intervals. Tools used to achieve this include Kegel exercises during waves of urgency or mental distraction techniques during these times.

Although used primarily for urge incontinence, scheduled voiding may also be helpful for those with SUI. For these patients, regularly scheduled urination leads to an empty bladder during a greater percentage of the day. Because some women will leak urine only if bladder volumes surpass specific threshold volumes, frequent emptying can significantly decrease incontinent episodes.

ESTROGEN REPLACEMENT

Estrogen has been shown to increase urethral blood flow and increase α-adrenergic receptor sensitivity, thereby increasing urethral coaptation and urethral closure pressure. In theory, estrogen may increase collagen deposition and increase vascularity of the periurethral capillary plexus. These are purported to improve urethral coaptation. Thus, for incontinent women who are atrophic, administration of exogenous estrogen is reasonable.

Estrogen is commonly administered topically. Many different regimens are appropriate and at our institution, we use conjugated equine estrogen cream (Premarin cream, Wyeth Pharmaceuticals, Philadelphia, PA) administered daily for 2 weeks, then twice weekly thereafter. Although no data are available to address the duration of treatment, women may be treated chronically with topical estrogen cream. Alternatively, oral estrogen may be prescribed if other menopausal symptoms for which estrogen would be beneficial co-exist (see Chap. 22, Summary of Current Use Indications).

However, despite these suggested benefits, a consensus regarding its beneficial effect on the lower urinary tract has not been as definitive. Specifically, studies have shown worsening or de novo development of urinary incontinence with systemic or topical estrogen administration (Hendrix, 2005; Jackson, 2006).

Treatment of Stress Urinary Incontinence

MEDICATIONS

Pharmaceutical treatment plays a minor role in the treatment of women with SUI. However, for women with mixed urinary incontinence, a trial of imipramine is reasonable to aid urethral contraction and closure. As discussed earlier, this tricyclic antidepressant has α-adrenergic effects and the urethra contains a high content of these receptors. Dosing can be found Table 23-5.

Table 23-5 Pharmacologic Treatment of Overactive Bladder				
Drug Name	**Brand Name**	**Drug Type**	**Dosage**	**Available Doses**
Oxybutynin (short-acting)	Ditropan	Antimuscarinic	2.5â€“5 mg PO tid	5-mg tablet, 5mg/mL syrup
Oxybutynin (long-acting)	Ditropan XL	See above	5â€“30 mg PO once daily	5-, 10-, 15-mg tablet
Oxybutynin (transdermal)	Oxytrol	See above	3.9 mg/d; patch changed twice weekly	36-mg patch
Tolterodine (short-acting)	Detrol	M_3 -selective antimuscarinic	1â€“2 mg PO bid	1-, 2-mg tablet
Tolterodine (long-acting)	Detrol LA	See above	2â€“4 mg PO once daily	2-, 4-mg capsule
Trospium chloride	Sanctura	Antimuscarinic quaternary amine	20 mg PO bid	20-mg tablet
Darifenacin	Enablex	M_3 -selective antimuscarinic	7.5â€“15 mg PO daily	7.5-, 15-mg tablet
Solifenacin	Vesicare	M_3 -selective antimuscarinic	5â€“10 mg PO once daily	5-, 10-mg tablets
Imipramine hydrochloride	Tofranil	Tricyclic antidepressant, anticholinergic, α -adrenergic, antihistamine	10â€“25 mg PO qdâ€“qid	10-, 25-, 50-mg tablets

bid = twice daily; PO = orally; qd = daily; qid = four times daily; tid = three times daily.

Recently, duloxetine (Cymbalta, Eli Lilly, Indianapolis, IN) a selective serotonin and norepinephrine reuptake inhibitor, has been evaluated for the treatment of SUI. In animal studies, serotonergic agonists suppress parasympathetic activity and enhance sympathetic and somatic activity. The sum effect promotes urine storage by relaxing the bladder and increasing outlet resistance. Although considered investigational, in randomized studies, this selective serotonin reuptake inhibitor (SSRI) has improved symptoms in women with SUI (Norton, 2002; Dmochowski, 2003a; Millard, 2004). Moreover, Ghoneim and co-workers (2005) in a randomized controlled trial evaluated the benefits of duloxetine, PFMT, and placebo combinations. Pad and quality of life data found the combination of duloxetine and PFMT to be more effective than either alone.

Previously, phenylpropanolamine (PPA) was used to treat SUI. However, in 2005, the Food and Drug Administration (FDA) reclassified PPA as category II and considered it as not generally safe or effective (U.S. Food and Drug Administration, 2005). Specifically, the FDA's decision was prompted by an increased rate of hemorrhagic strokes suffered by women taking this medication.

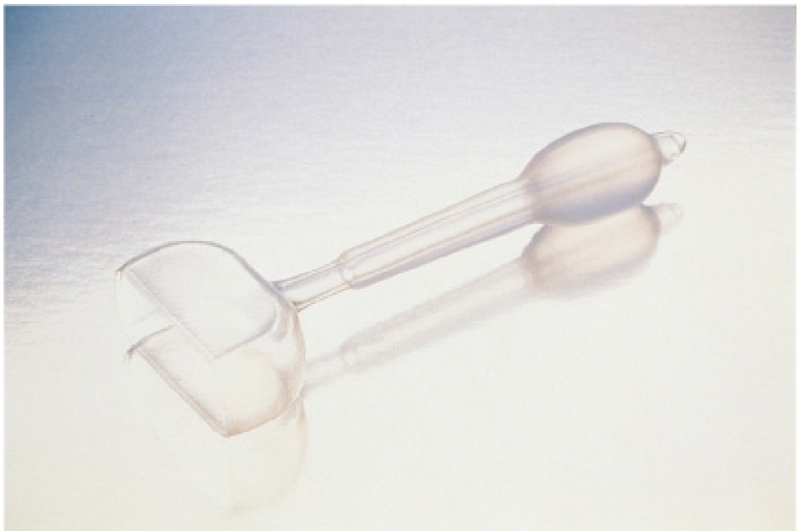
PESSARY AND URETHRAL INSERTS

Certain pessaries have been designed to treat incontinence as well as pelvic organ prolapse. Incontinence pessaries are designed to reduce downward excursion or funneling of the urethrovesical junction (see Chap. 24, Types of Pessaries). This provides bladder neck support and thereby helps to reduce incontinent episodes. Dependent on the amount of prolapse present, the efficacy of pessaries for treatment of urinary incontinence is variable. Not all women are appropriate candidates for pessaries, nor will all desire long-term management of incontinence or prolapse with these devices.

As an alternative to pessaries, a urethral insert may also be used for control of SUI. The only currently commercially available device is the *FemSoft* insert (Rochester Medical, Stewartville, MN) (Fig. 23-10). As the device is inserted, the sleeve slides into and

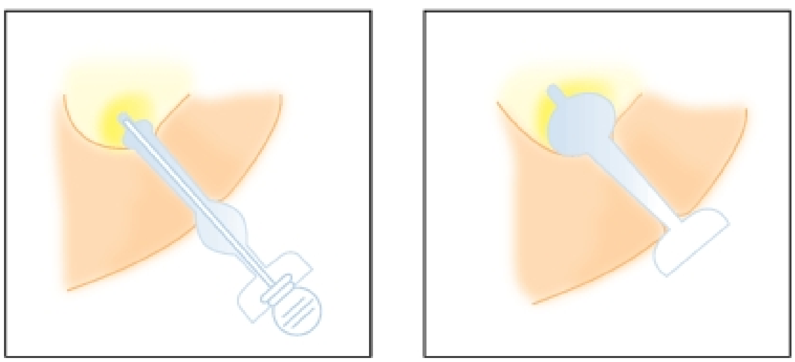
conforms to the urethra, creating a seal at the neck of the bladder to prevent accidental urine leakage. During routine bathroom visits, the insert is removed, discarded, and replaced with a fresh insert. Data are limited on the effectiveness of this insert. However, in an observational study of 150 women, Sirls and associates (2002) found significantly reduced rates of incontinence episodes.

FIGURE 23-10



A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

A. Urethral insert used for continence. *(Courtesy of Rochester Medical.)* The device consists of a short silicone tube that is covered by a mineral oilâ€"containing sheath. The proximal end of the conformable sheath expands to a bulbous tip. At the device's distal end, a soft flange prevents migration of the entire tube into the bladder. **B.** For insertion, an applicator is used to aid placement. With insertion, mineral oil within the sheath is evenly distributed along its length, and the bulbous tip is collapsed. When properly placed, the tip enters the bladder and the mineral oil preferentially flows to the device's bulbous tip. The applicator is then removed. As a result, the bulbous tip occludes the urethra to improve continence. When voiding is desired, the flange is grasped and the entire single-use device is gently removed. *(Redrawn from Sirls, 2002, with permission.)*

SURGICAL TREATMENT OF INTRINSIC SPHINCTERIC DEFICIENCY

Periurethral Bulking Agents

Periurethral injection of bulking agents is indicated for women who have urodynamic stress incontinence associated with intrinsic sphincteric deficiency. Additionally, it is a useful alternative in women with SUI who have multiple medical problems and who are thus poor surgical candidates.

Agents are injected submucosally and elevate the urethral mucosa to improve coaptation. A number of available bulking materials are available for injection. These materials can be injected periurethrally or transurethrally, and the location of the injections can vary. Some recommend two locations on either side of the urethra, whereas others advocate injections in three or four quadrants. At our institution, we usually inject at the level of the urethrovesical junction at sites of apparent urethral mucosal defects. However, if a global defect is noted or if a discrete defect is absent, then a two- to four-quadrant approach is used. The specific steps of injection and types of products used are described in Section 42-6, Urethral Bulking Injections.

SURGICAL TREATMENT OF ANATOMIC STRESS INCONTINENCE

For those who are not adequately improved with or do not desire conservative management, surgery may be an appropriate next step for successful treatment of stress incontinence symptoms. As noted earlier, urethral support is integral to continence. Thus, surgical procedures that recreate this support often diminish or cure incontinence. Over 200 procedures have been developed for the surgical correction of SUI, although the complete physiology underlying their success is not entirely clear. In general, these surgical procedures are believed to prevent bladder neck and proximal urethra descent during increases in intra-abdominal pressure.

Transvaginal Needle Procedures and Paravaginal Defect Repair

Surgeries that correct urethral hypermobility are theorized to prevent bladder neck and proximal urethra descent during increases in intra-abdominal pressure. In the 1960s through 1980s, needle suspension procedures such as the Raz, Pereyra, and Stamey techniques were popular surgical treatments for SUI, but have now largely been replaced by other methods. In brief, these surgeries used specially designed ligature carriers to place sutures through the anterior vaginal wall and/or periurethral tissues and suspend them to various levels of the anterior abdominal wall. These relied on the strength and integrity of the periurethral tissue and abdominal wall strength for successful suspension.

Although initial cure rates were satisfactory, the durability of these procedures decreased with time. Success rates range from 50 to 60 percent, well below rates found with other current anti-incontinence procedures (Moser, 2006). Failure stemmed largely from "pull-through" of sutures at the level of the anterior vaginal wall.

Abdominal paravaginal defect repair (PVDR) is a surgical procedure that corrects lateral support defects of the anterior vaginal wall. The technique involves suture attachment of the lateral vaginal wall to the arcus tendineus fascia pelvis and is illustrated in Section 42-14, Abdominal Paravaginal Defect Repair. Currently, PVDR is primarily a prolapse operation. Although previously used to correct SUI, long-term data have revealed that this is no longer a superior method for primary treatment of SUI (Colombo, 1996; Mallipeddi, 2001).

Retropubic Urethropexy

This group of procedures includes the Burch and Marshall-Marchetti-Krantz (MMK) colposuspension procedures, which involve suspension and anchorage of the pubocervical fascia to the musculoskeletal framework of the pelvis (see Section 42-2, Burch Colposuspension). Long considered the gold standard for surgical treatment of SUI, the Burch technique uses the strength of the iliopectineal ligament (Cooper ligament) to lift the anterior vaginal wall and the periurethral and perivesicular fibromuscular tissue. In contrast, during MMK surgery, the periosteum of the pubic bone is used to suspend these tissues. Complications commonly associated with these procedures include creation of de novo detrusor overactivity, urinary retention, and in the case of the MMK, osteitis pubis. A recent study has suggested that performing a Burch retropubic urethropexy at the time of an abdominal sacrocolpopexy for vaginal vault prolapse may significantly reduce the development of symptomatic postoperative stress urinary incontinence (see Chap. 24, Concomitant Prolapse and Incontinence Surgery).

Pubovaginal Slings

With this surgery, a strip of either rectus fascia or fascia lata is placed under the bladder neck through the retropubic space. The ends are secured at the level of the rectus abdominis fascia (see Section 42-5, Pubovaginal Sling). Previously, cadaveric fascia was used as the suspension material. However, this tissue is eventually degraded and found not to be durable over time (FitzGerald, 1999; Howden, 2006). Currently, autologous fascia is preferred and is obtained from the rectus sheath, although fascia lata from the thigh is an alternative.

This surgery is a standard procedure for SUI. It has traditionally been used for SUI stemming from intrinsic sphincteric deficiency. In addition, this procedure may also be indicated for patients with prior failed anti-incontinence operations. Albo and associates (2007) compared pubovaginal sling using autologous fascia with Burch colposuspension for SUI. Higher success rates were found with the sling procedure after 2 years. However, greater rates of difficulty voiding and creation of de novo urge incontinence were noted with pubovaginal sling.

Midurethral Slings

A surge of these slings appeared on the market in the late 1990s and early part of this decade. There are many different variations of these procedures but all involve the midurethral placement of synthetic mesh. Simplistically they are classified based on the route of placement and can be subdivided into those using a retropubic placement or a transobturator approach. Of these, popular procedures include: (1) tension free vaginal tape (TVT), a retropubic method; and (2) the transobturator tape (TOT), a transobturator method.

Midurethral slings provide several advantages. First, these techniques are effective and short-term cure rates approximate 90 percent (Lim, 2006). Of the two, retropubic and transobturator approaches appear to offer comparable short-term continence results (deTayrac, 2004; Morey, 2006; Sung, 2007). Laurikainen and co-workers (2007) randomly assigned 267 women to undergo either type and found equal rates of subjective and objective cure.

Despite these favorable comparisons, long-term data regarding the efficacy of transobturator approaches are yet to be available. However, data obtained 17 months postoperatively showed an incontinence improvement rate of 89 percent for those with preoperative SUI (Juma, 2007). In contrast, long-term continence rates are known with the retropubic technique and these approximate 80 percent (Nilsson, 2004).

In addition to their effectiveness, the recovery from midurethral sling placement is rapid, and many gynecologists provide this surgery on an outpatient basis. However, as with other anti-incontinence surgeries, general risks for midurethral sling procedures include urinary retention, lower urinary tract and vascular injuries, and creation of de novo voiding dysfunction such as urgency and retention.

Retropubic Approach

There are several commercial kits available for this procedure. Of these, one of the more commonly used is the TVT (Gynecare, Piscataway, NJ). With a retropubic approach, each trocar is placed through a vaginal suburethral incision lateral to the urethra and brought out suprapubically through two skin incisions (see Section 42-3, Tension-Free Vaginal Tape). Alternatively, needles may be placed through the space of Retzius and into the vagina, in a "top-down" approach.

Transobturator Approach

As with retropubic placement, different kits for this approach are produced by several companies. Each contains variations of needle and mesh design, but in general, a permanent sling material, usually polypropylene, is placed (Fig. 23-11). Sling material is directed bilaterally through the obturator foramen and underneath the mid-urethra. The entry point overlies the proximal tendon of the adductor longus muscle. Initially, the TOT was developed to avoid common TVT complications, that is, lower urinary tract injury and vascular injury, mainly in the space of Retzius.

FIGURE 23-11

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photograph of Monarc Subfascial Hammocktrocars. *(Courtesy of American Medical Systems.)*

The two major types of TOT procedures are defined by whether needle placement begins inside the vagina and is directed outward, termed an *in-to-out* approach, or alternatively starts outside and is directed inward, called an *out-to-in* approach (see Section 42-4, Transobturator Tape Sling). Initially, this procedure was developed with an out-to-in approach. However, with this approach, bladder and urethral injury were potential complications. For example, in a retrospective study, Abdel-Fattah and colleagues (2006) compared these two approaches. Lower urinary injury to the bladder or ureter complicated 1 percent of nearly 400 procedures and all followed the out-to-in technique.

As a result, the in-to-out approach was created and marketed with the assertion of decreased lower urinary tract injury rates. However, with the in-to-out technique, trocar tips travel closer to the obturator neurovascular bundle than with the out-to-in method (Achtari, 2006; Zahn, 2007). Thus, although each method has its theoretical advantages, the possibility of injury is not entirely eliminated.

Although the transobturator approach provides an effective day-surgery technique with potentially lower rates of bladder injury, some retrospective studies have suggested that they may have limited effectiveness for patients who demonstrate urodynamic criteria for intrinsic sphincteric deficiency (Miller, 2006; O'Connor, 2006).

New Innovations

Modification of the TVT procedure is seen with the TVT Secur. With this new technique, a 3- to 4-inch strip of polypropylene synthetic mesh is placed directly below the mid-urethra through a small vaginal incision. With this technique, mesh is not threaded

through the retropubic space and avoids the potential for vascular injury in this space. However, no data on efficacy or safety are currently available. Moreover, lower urinary tract injury is not completely averted with this method. Other techniques that have been introduced include microwave ablation of the periurethral tissues. However, current data do not support the efficacy or safety of this method.

Treatment of Urge Incontinence

ANTICHOLINERGIC MEDICATIONS

Oxybutynin and Tolterodine

Drugs that competitively bind to cholinergic receptors may improve symptoms of urge incontinence and include tolterodine, oxybutynin, and imipramine. However, as discussed earlier, muscarinic receptors are not limited to the bladder. Thus, side effects with these drugs may be significant. Of these, dry mouth, constipation, and blurry vision are the most common (Table 23-6). Patients frequently report that dry mouth is a primary reason for drug discontinuation. Importantly, anticholinergics are contraindicated in those with narrow-angle glaucoma. Because of these effects, the therapeutic objective of bladder M_3 blockade with these antimuscarinic agents is often limited by the anticholinergic side effects. Accordingly, drug selection should be tailored, and efficacy is balanced against tolerability. For example, Diokno and colleagues (2003) found oxybutynin (Ditropan XL, Ortho-McNeil Pharmaceuticals, Raritan, NJ) to be more efficacious than tolterodine (Detrol LA, Pfizer, New York, NY). However, tolterodine was associated with lower rates of side effects.

Table 23-6 Potential Anticholinergic Side Effects

Side Effect	Potential Clinical Consequence
Increased pupil size	Photophobia
Decreased visual accommodation	Blurred vision
Decreased salivation	Gingival and buccal ulceration
Decreased bronchial secretions	Small airway mucus plugging
Decreased sweating	Hyperthermia
Increased heart rate	Angina, myocardial infarction
Decreased detrusor function	Bladder distention and urinary retention
Decreased gastrointestinal mobility	Constipation

With oxybutynin, most side effects stem from its secondary metabolite that follows its liver metabolism. Therefore, to minimize side effects from oral oxybutynin, a transdermal patch was designed to decrease the first-pass effect of this drug. This leads to decreased liver metabolism and fewer systemic cholinergic side effects. Dmochowski and co-workers (2003b) found fewer anticholinergic side effects with transdermal oxybutynin compared with long-acting oral tolterodine.

Transdermal oxybutynin (Oxytrol, Watson Pharma, Morristown, NJ) is supplied as a 7.6 × 5.7-cm patch that is applied twice weekly to the abdomen, hip, or buttock. Each patch contains 36 mg of oxybutynin and delivers approximately 3.9 mg each day. Application site pruritus is the most common side effect, and varying the site of application may minimize skin reactions.

Selective Muscarinic Receptor Antagonists

Newer anticholinergic medications have been introduced that aim to reduce side effects, which in turn improves quality of life as well as patient compliance. The agents are all M_3 -receptor-selective antagonists and include solifenacin (VESIcare, Yamanouchi Pharma, Paramus, NJ), trospium chloride (Santura, Esprit Pharma, East Brunswick, NJ), and darifenacin (Enablex, Novartis, East

Hanover, NJ). Advantages of increased urgency warning time and decreased muscarinic side effects have been shown in randomized controlled studies (Cardozo, 2004; Chapple, 2005; Haab, 2006; Zinner, 2004). However, although the side-effect profile of these drugs is attractive, they have not been proved superior to nonselective muscarinic receptor drugs in randomized controlled trials.

Imipramine

This agent is less effective than tolterodine and oxybutynin, but displays α-adrenergic as well as anticholinergic characteristics. Therefore, it is occasionally prescribed for those with mixed urinary incontinence. Importantly, doses of imipramine used to treat incontinence are significantly lower than those used to treat depression or chronic pain. In our experience, this minimizes the theoretical risk of drug-related side effects.

SACRAL NEUROMODULATION

This outpatient surgically-implanted device contains a pulse generator and electrical leads that are placed into the sacral foramina to modulate innervation to the bladder and pelvic floor. Sacral neuromodulation is reserved for women with refractory urgency, frequency, or urge incontinence. It may be also considered for those with pelvic pain, interstitial cystitis, and defecatory dysfunction, although it is not FDA-approved for these indications. Sacral neuromodulation is not considered primary therapy, and women have typically exhausted pharmacologic and conservative options when considering it.

Implantation is typically a two-stage process. Initially, leads are placed and attached to an externally worn generator (see Section 42-12, Sacral Neuromodulation). After placement, frequency and amplitude of electrical impulses can be adjusted and tailored to maximize effectiveness. If a 50-percent or greater improvement in symptoms is noted, then internal implantation of a permanent pulse generator is planned.

Although its use is limited, this modality has been shown to be effective for treatment of urinary symptoms. Studies have found improvement rates ranging from 60 to 75 percent, and cure rates approximating 45 percent (Janknegt, 2001; Schmidt, 1999; Siegel, 2000). This procedure is minimally invasive and is typically completed in a day-surgery setting. Accordingly, recovery is rapid. Surgical complications are rare but may include pain or infection at the generator insertion site.

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EPIDEMIOLOGY

Pelvic organ prolapse is a health concern affecting millions of women worldwide. In the U.S., it is the third most common cited indication for hysterectomy. Moreover, a woman has an estimated lifetime risk of 11 percent to undergo surgery for prolapse or incontinence (Olsen, 1997). Despite the apparent prevalence of pelvic support problems, there are few studies of high epidemiologic quality to accurately estimate disease prevalence. This stems in part from a lack of consistent and valid clinical definitions (Weber, 2001a).

Although data are limited, studies show that the prevalence of pelvic organ prolapse increases steadily with age (Olsen, 1997; Swift, 2005). Given the condition's link to age and the changing demographics in the United States, the prevalence of pelvic floor disorders will undoubtedly grow.

RISK FACTORS

Table 24-1 summarizes predisposing factors for pelvic organ prolapse. Researchers agree that pelvic organ prolapse (POP) originates from multiple causes and develops gradually over a span of years. The relative importance, however, of each factor is not known.

Table 24-1 Risk Factors Associated with Pelvic Organ Prolapse
Pregnancy
Vaginal childbirth
Menopause
Aging
Hypoestrogenism
Chronically increased intra-abdominal pressure
Chronic obstructive pulmonary disease (COPD)
Constipation
Obesity
Pelvic floor trauma
Genetic factors
Race
Connective tissue disorders

Hysterectomy
Spina bifida

Obstetric-Related Risks

MULTIPARITY

Vaginal childbirth is the most frequently cited risk factor. There is no agreement whether it is pregnancy or parturition itself that predisposes to pelvic floor dysfunction. However, numerous studies have clearly shown that childbirth does increase a woman's propensity for developing POP. For example, in the Pelvic Organ Support Study (POSST), increasing parity was associated with advancing prolapse (Swift, 2005). Moreover, the risk of POP increased 1.2 times with each vaginal delivery. The Oxford family planning cohort study of 17,000 women showed that compared with nulliparous women, those with two deliveries had an eightfold increase in hospitalization for POP (Mant, 1997).

OTHER OBSTETRIC-RELATED RISKS

Although vaginal delivery is implicated in a woman's lifetime risk for POP, specific obstetric risk factors remain controversial. These include macrosomia, prolonged second-stage labor, episiotomy, anal sphincter laceration, epidural analgesia, forceps use, and oxytocin stimulation of labor. Each is a proposed risk factor, although not definitively proven. As we await further studies, we can anticipate that although each may have an important impact, it is the cumulative sum of all events occurring as the fetus traverses the birth canal that predisposes to POP.

Currently, two obstetric interventionsâ€”elective forceps delivery to shorten second-stage labor and elective episiotomyâ€”are not advocated because of a lack of evidence of benefit and their potential for maternal and fetal harm. First, forceps delivery is directly implicated in pelvic floor injury through its known association with anal sphincter laceration. Secondly, evidence of pelvic floor benefits from shortening the second stage of labor is lacking. For these reasons, elective forceps delivery is not recommended. Likewise, at least six randomized controlled trials comparing elective and selective episiotomy have shown no proven benefit, but an association with anal sphincter laceration, postpartum anal incontinence, and postpartum pain (Carroli, 2000).

ELECTIVE CESAREAN DELIVERY

Controversy has arisen over the topic of elective cesarean delivery to prevent pelvic floor dysfunction. Theoretically, if all women underwent cesarean delivery, there would be fewer women with pelvic floor dysfunction, including urinary incontinence and POP. Keeping in mind that most women do *not* develop pelvic floor dysfunction, elective cesarean delivery would subject many women to a potentially dangerous intervention who would otherwise not develop the problem. Specifically, given the 11 percent lifetime risk of undergoing surgery for incontinence or prolapse, for every one woman who would avoid pelvic floor surgery later in life by undergoing primary elective cesarean delivery, nine women would gain no benefit yet would nevertheless assume the potential risks of the cesarean. Most researchers agree that definitive recommendations will require further clinical studies to define the potential risks and benefits of elective cesarean delivery for primary prevention of pelvic floor dysfunction (Patel, 2006). At this point in time, recommendations regarding elective cesarean delivery to prevent pelvic floor dysfunction must be individualized.

Age

As described earlier, advancing age is also implicated in the development of POP. In the POSST study, there was a 100-percent increased risk of prolapse for each decade of life. In women aged 20 to 59 years, the incidence of POP roughly doubles with each decade. As with other risks for POP, aging is a complex process. The increased incidence may result from physiologic aging and degenerative processes as well as hypoestrogenism. Separating the effects of estrogen deprivation from the effects of the aging process is problematic.

Connective Tissue Disease

Women with connective tissue disorders may be more likely to develop POP. In a small case series study, one third of women with Marfan syndrome and three fourths of women with Ehlers-Danlos syndrome reported a history of POP (Carley, 2000).

Race

Racial differences in POP prevalence have been demonstrated in several studies (Schaffer, 2005). Black and Asian women show the lowest risk, whereas Hispanic women appear to have the highest risk (Kim, 2005). Although differences in collagen content have been demonstrated between races, racial differences in the bony pelvis may also play a role. For instance, black women more commonly have a narrow pubic arch and an android or anthropoid pelvis. These shapes are protective against POP compared with the gynecoid pelvis typical of most Caucasian women.

Increased Abdominal Pressure

Chronically increased intra-abdominal pressure is believed to play a role in POP pathogenesis. This condition is present with obesity, chronic constipation, chronic coughing, and repetitive heavy lifting. Numerous studies identify obesity as an independent risk factor for stress urinary incontinence (Brown, 1996; Burgio, 1991; Dwyer, 1988). However, the association with the development of POP is less clear (Hendrix, 2002; Nygaard, 2004). With regard to lifting, a Danish study demonstrated that nursing assistants who were involved with repetitive heavy lifting were at increased risk to undergo surgical intervention for prolapse, with an odds ratio of 1.6 (Jorgensen, 1994). In addition, cigarette smoking and chronic obstructive pulmonary disease (COPD) have also been implicated in the development of POP, although few data support this association (Gilpin, 1989; Olsen, 1997). Similarly, although chronic coughing results in repetitive increases in intra-abdominal pressure, no clear mechanism has been demonstrated. Some believe that the inhaled chemical compounds in tobacco may cause changes that lead to POP rather than the chronic cough itself (Wieslander, 2005).

DESCRIPTION AND CLASSIFICATION

Visual Descriptors

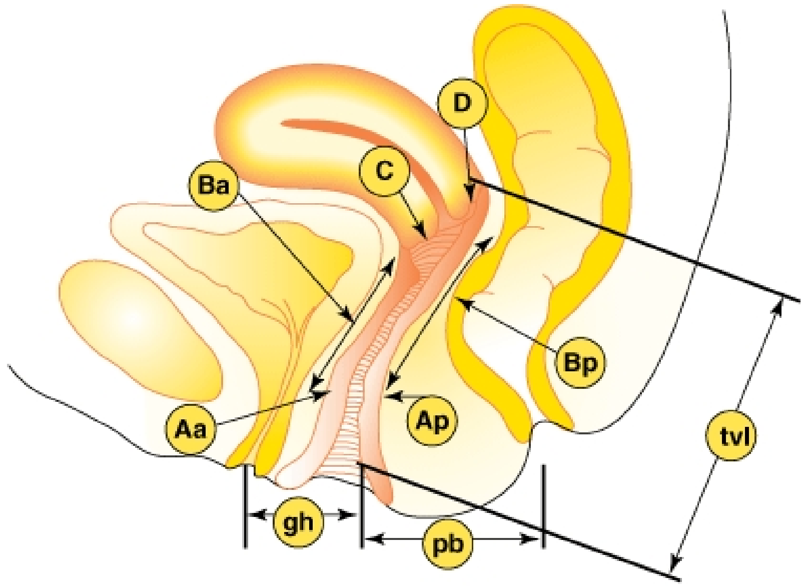
Prolapse is the downward displacement of one of the pelvic organs from its normal location that results in vaginal wall protrusion or bulge. The terms *cystocele, cystourethrocele, uterine prolapse, rectocele,* and *enterocele* have traditionally been used to describe the protrusion location. In specifying an organ, these terms imply that a vaginal bulge is with certainty caused by a herniation of the bladder, bladder/urethra, uterus, rectum, or small bowel, respectively. However, these terms are imprecise and misleading, as they focus on what is presumed to be prolapsed rather than what is actually seen. More importantly, such assumptions can lead to unforeseen problems. For example, a posterior vaginal prolapse that is presumed to be a rectocele may require an alternative reconstructive repair if an undetected enterocele is discovered at the time of surgery.

Although these terms are deeply entrenched in the literature, it is more clinically useful to describe prolapse in terms of what one actually sees: anterior vaginal wall prolapse, apical vaginal wall prolapse, cervical prolapse, posterior vaginal wall prolapse, perineal prolapse, and rectal prolapse. These descriptors do not presuppose what is behind the vaginal wall, but rather describe the tissues that are objectively noted to be prolapsed.

Pelvic Organ Prolapse Quantification (POP-Q)

In 1996, the International Continence Society defined a system of Pelvic Organ Prolapse Quantification (POP-Q) (Bump, 1996). Demonstrating high intra- and interexaminer reliability, the POP-Q system is a major advance in studying prolapse. It allows researchers to report findings in a standardized, easily reproducible fashion. This system contains a series of site-specific measurements of a woman's pelvic organ support. Prolapse in each segment is measured relative to the hymen, which is a fixed anatomic landmark that can be identified consistently. Six points are located with reference to the plane of the hymen: two on the anterior vaginal wall (points Aa and Ba), two in the apical vagina (points C and D), and two on the posterior vaginal wall (points Ap and Bp) (Fig. 24-1). All POP-Q points, except total vaginal length (tvl), are measured during patient Valsalva and should reflect maximum protrusion.

FIGURE 24-1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Drawing displays the anatomic landmarks used during pelvic organ prolapse quantification (POP-Q).

ANTERIOR VAGINAL WALL POINTS

Point Aa

This term defines a point that lies in the midline of the anterior vaginal wall and is 3 cm proximal to the external urethral meatus. This corresponds to the proximal location of the urethrovesical crease. In relation to the hymen, this point's position ranges, by definition, from â€"3 (normal support) to +3 cm (maximum prolapse of point Aa).

Point Ba

This point represents the most distal position of any part of the upper anterior vaginal wall from the vaginal cuff or anterior vaginal fornix to point Aa. It is â€"3 cm in the absence of prolapse. In a woman with total vaginal eversion post-hysterectomy, Ba would have a positive value equal to the position of the cuff from the hymen.

APICAL VAGINAL POINTS

Point C

The two apical points, C and D, which are located in the proximal vagina, represent the most proximal locations of a normally positioned lower reproductive tract. Point C defines a point that is at either the most distal edge of the cervix or the leading edge of the vaginal cuff after total hysterectomy.

Point D

This term defines a point that represents the location of the posterior fornix in a woman who still has a cervix. It is omitted in the absence of a cervix. This point represents the level of uterosacral ligament attachment to the proximal posterior cervix and thus differentiates uterosacral-cardinal ligament support failure from cervical elongation. The *total vaginal length* (TVL) is the greatest depth of the vagina in centimeters when point C or D is reduced to its fullest position.

POSTERIOR VAGINAL WALL POINTS

Point Ap

This term defines a point in the midline of the posterior vaginal wall that lies 3 cm proximal to the hymen. Relative to the hymen, this point's range of position is by definition â€"3 (normal support) to +3 cm (maximum prolapse of point Ap).

Point BP

This point represents the most distal position of any part of the upper posterior vaginal wall from the vaginal cuff or posterior vaginal fornix to point Bp. By definition, this point is at â€"3 cm in the absence of prolapse. In a woman with total vaginal eversion post-hysterectomy, Bp would have a positive value equal to the position of the cuff from the hymen.

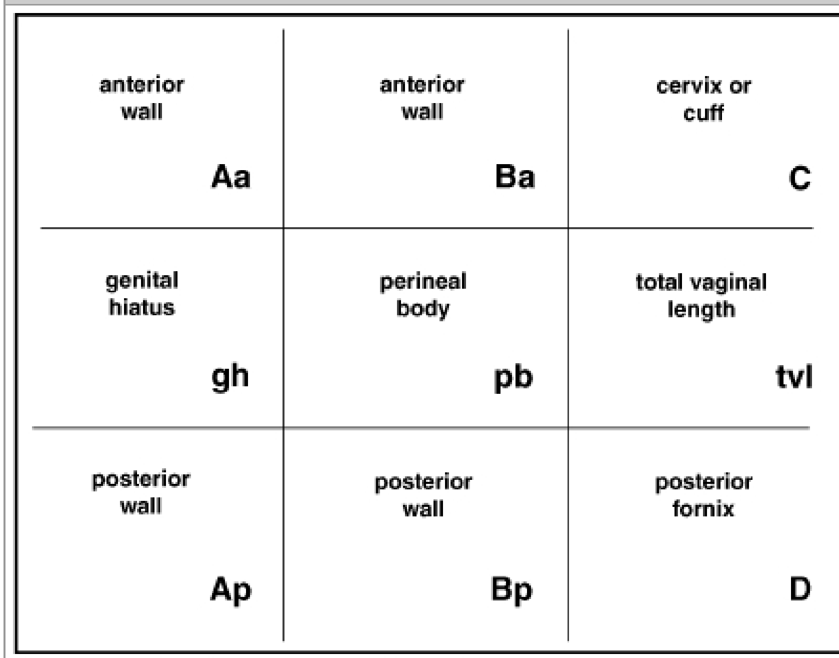
Genital Hiatus and Perineal Body

In addition to the hymen, remaining measurements include those of the genital hiatus (gh) and the perineal body (pb) (see Fig. 24-1). The genital hiatus is measured from the middle of the external urethral meatus to the midline of the posterior hymenal ring. The perineal body is measured from the posterior margin of the genital hiatus to the mid-anal opening.

ASSESSMENT WITH POP-Q

With the hymenal plane defined as zero, the anatomic position of these points from the hymen is measured in centimeters. Points above or proximal to the hymen and are described with a negative number. Positions below or distal to the hymen are noted using a positive number. The point measurements can be organized using a three-by-three grid as shown in Fig. 24-2. Normal support is contrasted with complete post-hysterectomy vaginal eversion in Fig. 24-3, whereas Fig. 24-4 contrasts anterior with posterior vaginal wall prolapse.

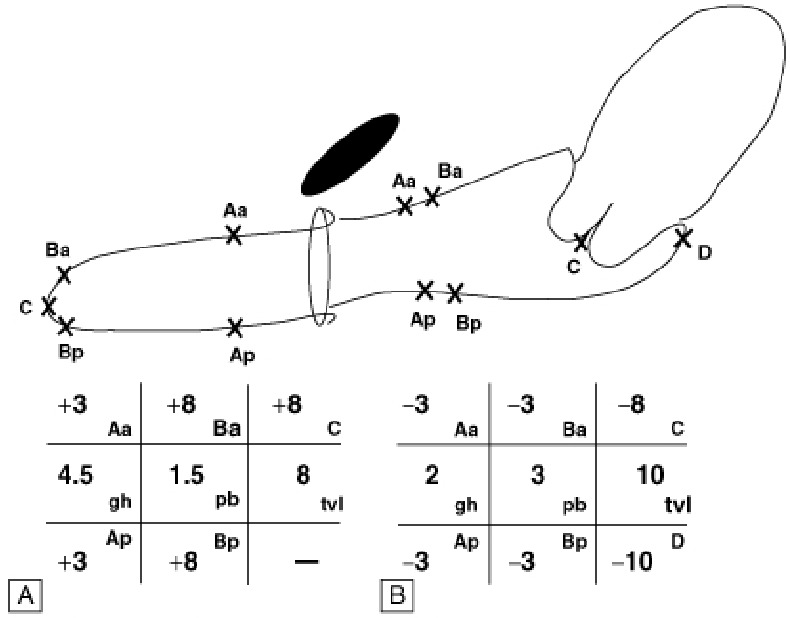
FIGURE 24-2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

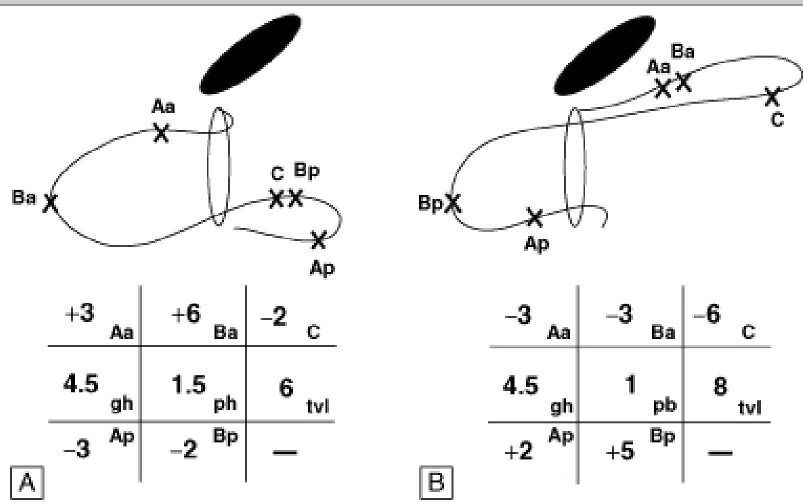
Grid system used for charting in pelvic organ prolapse quantification (POP-Q).

FIGURE 24-3



Drawing and corresponding POP-Q scoring grid of complete vaginal prolapse (**A**). This contrasts with grid **B,** which shows measurements that are found in women with normal support. *(Redrawn from Bump, 1996, with permission.)*

FIGURE 24-4



Grid and drawing of an anterior support defect **(A)** and posterior support defect **(B)** . *(Redrawn from Bump, 1996, with permission.)*

The degree of prolapse can also be quantified using a five-stage ordinal system as summarized in Table 24-2 (Bump, 1996). Stages are assigned according to the most severe portion of the prolapse.

Table 24-2 The Pelvic Organ Prolapse Quantification (POP-Q) Staging System of Pelvic Organ Support	
Stage 0:	No prolapse is demonstrated. Points Aa, Ap, Ba, and Bp are all at â€“3 cm and either point C or D is between â€“TVL (total vaginal length) cm and â€“(TVLâ€“2) cm (i.e., the quantitation value for point C or D is ≤ â€“[TVL â€“ 2] cm). Fig. 24â€“3B represents stage 0.
Stage I:	The criteria for stage 0 are not met, but the most distal portion of the prolapse is >1 cm above the level of the hymen (i.e., its quantitation value is < â€“ 1 cm).
Stage II:	The most distal portion of the prolapse is ≤1 cm proximal to or distal to the plane of the hymen (i.e., its quantitation value is ≥â€“1 cm but ≤+1 cm).
Stage III:	The most distal portion of the prolapse is >1 cm below the plane of the hymen but protrudes no further than 2 cm less than the total vaginal length in centimeters (i.e., its quantitation value is > + 1 cm but < + [TVLâ€“2] cm). Fig. 24â€“4A represents stage III Ba and Fig. 24â€“4B represents stage III Bp prolapse.
Stage IV:	Essentially, complete eversion of the total length of the lower genital tract is demonstrated. The distal portion of the prolapse protrudes to at least (TVLâ€“2) cm (i.e., its quantitation value is ≥ +[TVLâ€“2] cm). In most instances, the leading edge of stage IV prolapse will be the cervix or vaginal cuff scar. Fig. 24â€“3A represents stage IV C prolapse.

From Bump, 1996, with permission.

Baden-Walker Halfway System

This descriptive tool is also used to classify prolapse on physical examination and is in widespread clinical use. Although not as informative as the POP-Q, it is adequate for clinical use if each compartment (anterior, apical, and posterior) is evaluated (Table 24-3) (Baden, 1972).

Table 24-3 Baden-Walker Halfway System for the Evaluation of Pelvic Organ Prolapse on Physical Examination[a]
Grade
Grade 0 Normal position for each respective site
Grade 1 Descent halfway to the hymen
Grade 2 Descent to the hymen
Grade 3 Descent halfway past the hymen
Grade 4 Maximum possible descent for each site

[a] Descent of the anterior vaginal wall, posterior vaginal wall, or apical prolapse can be graded with this system.

From Baden, 1992, with permission.

PATHOPHYSIOLOGY

Pelvic organ support is maintained by complex interactions between the levator ani muscle, vagina, and pelvic floor connective tissue. However, these mechanisms have not been fully delineated.

When the levator ani muscle has normal tone and the vagina has adequate depth, the upper vagina lies nearly horizontal in the standing female (see Fig. 38-9). This creates a "flap-valve" effect in which the upper vagina is compressed against the levator plate

during periods of increased intra-abdominal pressure. It is theorized that when the levator ani muscle loses tone, the vagina drops from a horizontal to a semi-vertical position. This widens or opens the genital hiatus and predisposes pelvic viscera to prolapse. Without adequate levator ani support, the visceral fascial attachments of the pelvic contents are placed on tension and are thought to stretch and eventually fail.

Mechanism of Levator Ani Damage

Skeletal muscle is a dynamic tissue that is constantly remodeling and regenerating. A heterogeneous population of fibers with different functions allows skeletal muscle to adapt to different situations, such as stretch and mechanical load. Damage to the levator ani muscles follows direct muscle tissue injury or may result from damage to its nerve supply. Labor and vaginal delivery has the potential to cause this type of damage. However, it is unclear what effect other pathologic conditions, such as chronically increased intra-abdominal pressure, may have on the levator ani muscle.

DIRECT INJURY

Direct injury to the levator ani muscles is believed to occur during second-stage labor. The muscle undergoes significant stretch as the fetal head distends the pelvic floor. Specifically, computer-simulated models that recreate labor stresses show that, of the levator ani muscles, the medial pubococcygeus muscles undergo the most stretch (Lien, 2004). Moreover, Tunn and associates (1999) used magnetic resonance (MR) imaging to describe the levator ani muscle after vaginal delivery in 14 women. They found the urogenital and levator hiatus areas to be increased immediately postpartum compared with second scans obtained 2 weeks later. This suggests that the levator ani muscles actually remodel and recover in some women after vaginal delivery.

This appears to be true functionally as well. Postpartum women have been found to have decreased pelvic floor muscle strength after delivery but have return of function by 10 weeks (Peschers, 1997). However, it is also likely that in some cases permanent stretch injury occurs. Evidence for this is suggested by the clinical observation that multiparous women have a widened genital hiatus compared with nulliparous women.

NEUROLOGIC INJURY

Nerve injury is a suspected risk factor for POP. In addition to anatomic studies, pudendal nerve terminal motor latencies (PNTML) and electromyography (EMG), described in Chapter 25, Electromyography, have been used to investigate neural damage after vaginal delivery. From these studies, there is evidence that pudendal neuropathy is associated with vaginal delivery (Snooks, 1990). It is proposed that stretch injury of the pudendal nerve occurs during second-stage labor because the nerve is fixed as it exits Alcock canal (see Fig. 38-30) (Benson, 1999). Alternatively, chronic straining with defecation has also been associated with pelvic muscle denervation (Jones, 1987; Lubowski, 1988; Snooks, 1985). Excess straining and perineal descent can stretch the pudendal nerves and result in neuropathy (Kiff, 1984). However, despite these associations between neuropathy and vaginal delivery or chronic constipation, data supporting an association or causation between pudendal neuropathy and POP are lacking (Barber, 2002; Snooks, 1985).

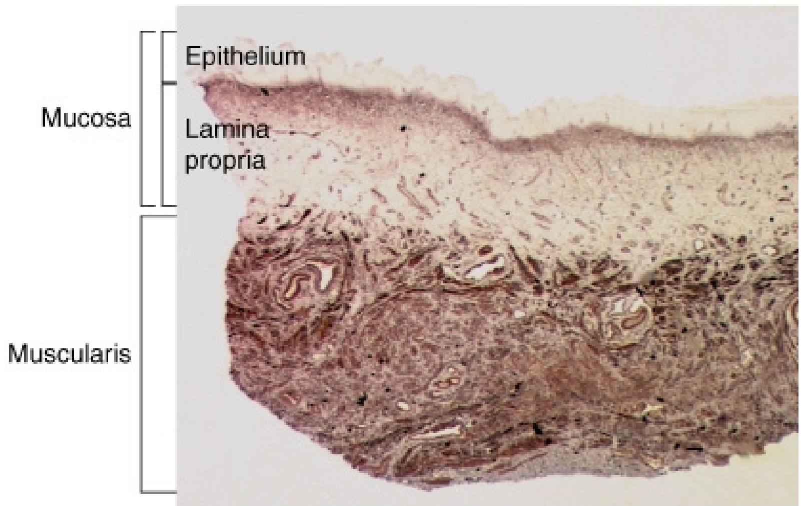
Mechanism of Vaginal Wall Injury

The vaginal wall is comprised of squamous epithelium, smooth muscle muscularis, and adventitia. All elements are embedded in an extracellular matrix that includes collagen, elastin fibers, and smooth muscle. Abnormalities of these components may contribute to vaginal dysfunction and development of POP.

SITE-SPECIFIC DEFECTS

This theory is based on the premise that tears in the "endopelvic fascia" surrounding the vaginal wall allow herniation of the pelvic organs. The association of POP with vaginal delivery is consistent with this theory. However, study of the microscopic anatomy of the vaginal wall indicates that endopelvic fascia does not exist as a specific anatomic tissue, but rather represents the fibromuscular layer of the vaginal wall, that is, vaginal muscularis and adventitia (Fig. 24-5) (Boreham, 2001).

FIGURE 24-5



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photomicrograph shows a complete cross section of the vaginal wall. The fibromuscular layer is comprised of muscularis and adventitia, which lies deep to the muscularis. *(Courtesy of Dr. Ann Word.)*

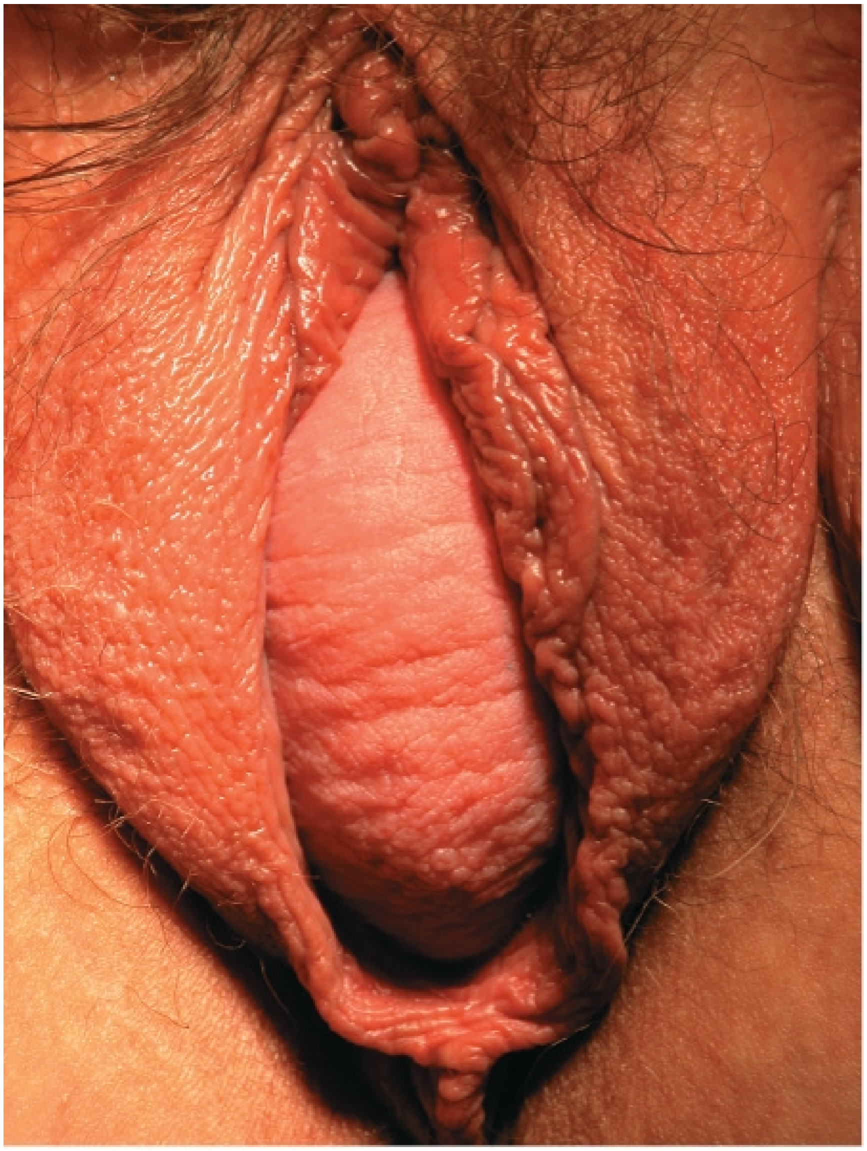
Although most researchers agree that vaginal delivery predisposes women to POP, there is less agreement regarding changes in the pelvic musculature and vaginal wall that result in prolapse. Nichols and Randall (1989) proposed an attenuation of the vaginal wall without loss of fascial attachments. They term prolapse of this type as *distention* cystocele or rectocele (Fig. 24-6). In contrast, anterior and posterior wall defects due to loss of the connective tissue attachment of the lateral vaginal wall to the pelvic side wall are described as *displacement* (paravaginal) cystocele or rectocele (Fig. 24-7). With distention type prolapse, the vaginal wall appears smooth and without rugae, due to attenuation. With displacement type prolapse, vaginal rugae are visible. Both defect types could result from the stretching or tearing of support tissues during second-stage labor.

FIGURE 24-6

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photograph shows midline or distension cystocele. Note the characteristic loss of vaginal wall rugae.

FIGURE 24-7



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photograph shows a lateral cystocele, also termed paravaginal or displacement cystocele. Rugae are present, which indicates that loss of support is lateral rather than central.

SMOOTH MUSCLE DYSFUNCTION

Abnormalities in the anatomy, physiology, and cellular biology of vaginal wall smooth muscle may contribute to POP. For example, smooth muscle fibers arising from the vaginal wall attach to the levator ani complex (DeLancey, 1990). Dysfunction of this smooth muscle may affect the attachment of the lateral vagina to the pelvic side wall. Additionally, the fraction of smooth muscle in the muscularis of the anterior and posterior vaginal wall apex in women with prolapse is decreased compared with women without prolapse (Boreham, 2002a, 2002b). Decreased smooth muscle content of the round ligament in women with POP has also been described (Ozdegirmenci, 2005).

CONNECTIVE TISSUE ABNORMALITIES

The connective tissue of the pelvis is comprised of collagen, elastin, smooth muscle, and microfibers, which are anchored in an

extracellular matrix of polysaccharides. The connective tissue that invests the pelvic organs provides substantial anatomic support of the pelvis and its contents. There is evidence that suggests abnormalities of connective tissue and connective tissue repair may predispose women to prolapse (Norton, 1995; Smith 1989). Women with connective tissue disorders such as Ehlers-Danlos or Marfan syndrome are more likely to develop POP and urinary incontinence (Carley, 2000; Norton, 1995).

Decreased collagen content is found in women with stress urinary incontinence and POP. Compared with women displaying normal pelvic organ support, those with prolapse were found to have less total collagen in their "pubocervical fascia" as well as a weaker type of collagen (Jackson, 1996; Makinen, 1986). This may be secondary to increased collagen degradation. Specifically, analysis of collagen in prolapsing tissue has found structural, biochemical, and quantitative differences in collagen content (Boreham, 2001).

The fascia and connective tissues of the pelvic floor may also lose strength consequent to aging and loss of neuroendocrine signaling in pelvic tissues (Smith, 1989). Estrogen deficiency can affect the biomedical composition, quality, and quantity of collagen. Estrogen influences collagen content by increasing synthesis or decreasing degradation. Exogenous estrogen supplementation has been found to increase the skin collagen content in postmenopausal women who are estrogen deficient (Brincat, 1983). Estrogen supplementation prior to prolapse surgery, and/or postoperatively, is considered essential by many prolapse surgeons. Although this practice may seem logical and empirically sound, no evidence exists to suggest improved surgical outcomes with this use of adjuvant estrogen.

Levels of Vaginal Support

The vagina consists of a fibromuscular, flattened, cylindrical tube with three levels of support, as described by DeLancey (1992) (see Fig. 38-11). Level I support suspends the upper or proximal vagina. Level II support attaches the mid-vagina along its length to the arcus tendineus fascia pelvis. Level III support results from fusion of the distal vagina to adjacent structures. Defects in each level of support result in identifiable vaginal wall prolapse: anterior, apical, and posterior.

It is notable that the three levels of support are interconnected through a loose fibromuscular connective tissue network. As it envelops the pelvic organs, this fibromuscular connective tissue network connects these organs loosely to supportive musculature and bony pelvis. Composed of collagen, elastin, adipose tissue, nerves, blood vessels, lymphatic channels, and smooth muscle, this loose fibromuscular connective tissue network provides stabilization and support, yet allows mobility, expansion, and contraction of viscera. As such, normal pelvic support is provided by complex interaction between the pelvic floor muscles, connective tissue attachments, and the bony pelvis.

LEVEL I SUPPORT

This level consists of the cardinal and uterosacral ligaments attachment to the cervix and upper vagina. The cardinal ligaments fan out laterally and attach to the parietal fascia of the obturator internus and piriformis muscles, the anterior border of the greater sciatic foramen, and the ischial spines. The uterosacral ligaments are posterior fibers that attach to the presacral region at the level of S2 through S4. Together, this dense visceral connective tissue complex maintains vaginal length and horizontal axis. It allows the vagina to be supported by the levator plate and positions the cervix just superior to the level of the ischial spines. Defects in this support complex may lead to apical prolapse. This is frequently associated with small bowel herniation into the vaginal wall, that is, enterocele.

LEVEL II SUPPORT

This support consists of the paravaginal attachments that are contiguous with the cardinal/uterosacral complex at the ischial spine. These are the connective tissue attachments of the lateral vagina anteriorly to the arcus tendineus fascia pelvis and posteriorly to the arcus tendineus rectovaginalis. Detachment of this connective tissue from the arcus tendineus fascia pelvis leads to lateral or paravaginal anterior vaginal wall prolapse.

LEVEL III SUPPORT

The perineal body, superficial and deep perineal muscles, and fibromuscular connective tissue comprise level III. Collectively, these support the distal one-third of the vagina and introitus. The perineal body is essential for distal vaginal support as well as proper function of the anal canal. Damage to level III support contributes to anterior and posterior vaginal wall prolapse, gaping introitus,

and perineal descent.

EVALUATION OF THE PATIENT WITH PELVIC ORGAN PROLAPSE

Symptoms Associated with Pelvic Organ Prolapse

Pelvic organ prolapse involves multiple anatomic and functional systems, and is commonly associated with genitourinary, gastrointestinal, and musculoskeletal symptoms (Table 24-4). Prolapse rarely results in severe morbidity or mortality, however, it can greatly diminish quality of life. Therefore, initial evaluation must include a careful assessment of prolapse-related symptoms and their affect on activities of daily living.

Table 24-4 Symptoms Associated with Pelvic Organ Prolapse

Symptoms	Other Possible Causes
Bulge symptoms	
Sensation of vaginal bulging or protrusion	Rectal prolapse
Seeing or feeling a vaginal or perineal bulge	Vulvar or vaginal cyst/mass
Pelvic or vaginal pressure	Pelvic mass
Heaviness in pelvis or vagina	Hernia (inguinal or femoral)
Urinary symptoms	
Urinary incontinence	Urethral sphincter incompetence
Urinary frequency	Detrusor overactivity
Urinary urgency	Hypoactive detrusor function
Weak or prolonged urinary stream	Bladder outlet obstruction (i.e., postsurgical)
Hesitancy	Excessive fluid intake
Feeling of incomplete emptying	Interstitial cystitis
Manual reduction of prolapse to start or complete voiding	Urinary tract infection
Position change to start or complete voiding	
Bowel symptoms	
Incontinence of flatus or liquid/solid stool	Anal sphincter disruption or neuropathy
Feeling of incomplete emptying	Diarrheal disorder
Hard straining to defecate	Rectal prolapse
Urgency to defecate	Irritable bowel syndrome
Digital evacuation to complete defecation	Rectal inertia
Splinting vagina or perineum to start or complete defecation	Pelvic floor dyssynergia

Feeling of blockage or obstruction during defecation	Hemorrhoids
	Anorectal neoplasm
Sexual symptoms	
Dyspareunia	Vaginal atrophy
Decreased lubrication	Levator ani syndrome
Decreased sensation	Vulvodynia
Decreased arousal or orgasm	Other female sexual disorder
Pain	
Pain in vagina, bladder, or rectum	Interstitial cystitis
Pelvic pain	Levator ani syndrome
Low back pain	Vulvodynia
	Lumbar disc disease
	Musculoskeletal pain
	Other causes of chronic pelvic pain

From Barber, 2005a, with permission.

Symptoms should be carefully reviewed to determine if they are caused by the prolapse or by other etiologies. For example, bulge or pressure symptoms are often the direct result of prolapse. In contrast, chronic straining during defecation may be a cause rather than a result of prolapse. A thorough history and physical examination will often help delineate the relationship between POP and symptoms.

During symptom inventory, several tools may be useful in assessing severity. Two commonly used questionnaires are the Pelvic Floor Distress Inventory (PFDI) and the Pelvic Floor Impact Questionnaire (PFIQ) (Barber, 2005b). The PFDI assesses urinary, colorectal, and prolapse symptoms, whereas the PFIQ assesses the impact of prolapse on quality of life (Tables 24-5 and 24-6).

Table 24-5 Short Form: Pelvic Floor Impact Questionnaire 7-Item (PFIQ-7)

Please select the best answer to each question below.

Name ______________________________

Has your prolapse affected your:

1. Ability to do household chores (cooking, house cleaning, laundry)?
   _ Not at all _ Mildly _ Moderately _ Severely
2. Physical recreation such as walking, swimming, or other exercises?
   _ Not at all _ Mildly _ Moderately _ Severely
3. Entertainment activities (movies, church)?
   _ Not at all _ Mildly _ Moderately _ Severely
4. Ability to travel by car or bus more than 30 minutes from home?
   _ Not at all _ Mildly _ Moderately _ Severely
5. Participation in social activities outside your home?
   _ Not at all _ Mildly _ Moderately _ Severely
6. Emotional health (nervousness, depression)?
   _ Not at all _ Mildly _ Moderately _ Severely
7. Feeling frustrated?
   _ Not at all _ Mildly _ Moderately _ Severely

From Flynn, 2006, with permission.

Table 24-6 Short Form: Pelvic Floor Distress Inventory 22-Item (PFDI-22)[a]
POPDIâ€"6
Do you usually_____________, and if so how much are you bothered by: 1. experience pressure in the lower abdomen 2. experience heaviness or dullness in the abdomen or genital area 3. have a bulge or something falling out that you can see or feel in the vaginal area 4. have to push on the vagina or around the rectum to have or complete a bowel movement 5. experience a feeling of incomplete bladder emptying 6. have to push up on a bulge in the vaginal area with your fingers to start or complete urination
CRADIâ€"8
_____________, and if so how much are you bothered by it? 1. Do you usually feel you need to strain too hard to have a bowel movement 2. Do you usually feel you have not completely emptied your bowels at the end of bowel movement 3. Do you usually lose stool beyond your control if your stool is well formed 4. Do you usually lose stool beyond your control if your stool is loose or liquid 5. Do you usually lose gas from the rectum beyond your control 6. Do you usually have pain when you pass your stool 7. Do you usually experience a strong sense of urgency and have to rush to the bathroom to have abowel movement 8. Does part of your bowel ever pass through the rectum and bulge outside during or after a bowel movement
UDIâ€"8
Do you usually have _____________, and if so, how much are you bothered by: 1. frequent urination 2. leakage related to feeling of urgency 3. leaking related to activity, coughing, or sneezing 4. leakage when you go from sitting to standing 5. small amounts of urine leakage (i.e., drops) 5. difficulty emptying the bladder 7. pain or discomfort in the lower abdomen or genital area 8. pain in the middle of your abdomen as your bladder fills

[a] For each question, patients fill in the blank with each phrase underneath the question. The same multiple choice responses (not at all, mildly, moderately, and severely) used for the PFIQ-7 are used for the PFDI-22.

From Flynn, 2006, with permission.

Treatment is symptom-directed and in the absence of complaints, prolapse generally does not require therapy. However, for those with symptoms, treatment may include both nonsurgical and surgical therapy.

BULGE SYMPTOMS

Two of the most common symptoms associated with prolapse are the sensation or visualization of a vaginal or perineal protrusion, and the sensation of pelvic pressure. Women with these symptoms often complain of feeling a ball in the vagina, sitting on a weight, or noting a bulge rubbing on their clothes. These symptoms appear to worsen with prolapse progression (Ellerkmann, 2001). If bulge symptoms are the primary complaint, successful replacement of the prolapse with nonsurgical or surgical therapy will usually provide adequate treatment.

URINARY SYMPTOMS

Patients with POP often have concurrent urinary symptoms including stress urinary incontinence (SUI), urge urinary incontinence, frequency, urgency, urinary retention, recurrent urinary tract infection, or voiding dysfunction. Although these symptoms may be caused or exacerbated by prolapse, it should not be assumed that surgical or nonsurgical correction of prolapse will be curative. For example, irritative bladder symptoms (frequency, urgency, and urge urinary incontinence) do not reliably improve with replacement of prolapse and sometimes worsen after surgical management. Moreover, they may be unrelated to the prolapse and require alternative therapy. In contrast, urinary retention has been found to improve with prolapse treatment if the symptom is due to an obstructed urethra (FitzGerald, 2000).

For these reasons, urodynamic testing is a valuable adjunct in women with urinary symptoms who are undergoing treatment of prolapse (see Chap. 23, Cystometrics). This testing attempts to determine the relationship between urinary symptoms and POP and will help guide therapy. Additionally, consideration may also be given to temporarily placing a pessary prior to surgery to determine if urinary symptoms improve, and thereby predict whether surgical reduction of prolapse will be beneficial.

GASTROINTESTINAL SYMPTOMS

Constipation is often present in women with pelvic organ prolapse. However, replacement of prolapse either by surgical repair or with a pessary does not usually cure constipation and may actually worsen it. In one study of defect-directed posterior repair, constipation resolved postoperatively in only 43 percent of patients (Kenton, 1999). Therefore, if a patient's primary symptom is constipation, treatment of prolapse may not be indicated. Constipation should be viewed as a problem distinct from prolapse and evaluated separately (see Chap. 25, Rectoanal inhibitory reflex).

The need for digital decompression of the posterior vaginal wall, the perineal body, or the distal rectum to evacuate the rectum is the most common defecatory symptom associated with posterior vaginal wall prolapse (Barber, 2003; Burrows, 2004; Ellerkmann, 2001). Surgical approaches to this problem result in variable success, with symptom resolution rates as low as 36 percent (Kenton, 1999).

Anal incontinence of flatus or liquid or solid stool may also be seen in conjunction with POP. On occasion, prolapse may lead to stool trapping in the distal rectum with subsequent leakage of liquid stool around retained feces. If symptoms are present, a full anorectal evaluation should be performed (see Chap. 25, Physical Examination). Most types of anal incontinence would not be expected to improve with surgical repair of prolapse. However, if evaluation reveals an anal sphincter defect as the cause of anal incontinence, anal sphincteroplasty may be performed concurrently with prolapse repair.

SEXUAL DYSFUNCTION

Sexual dysfunction is often seen in women with POP. The etiology is frequently multifactorial and includes psychosocial factors, urogenital atrophy, aging, and male sexual dysfunction (see Chap. 13, Female Sexuality). Studies related to sexual function in women with prolapse are limited. In one study, a validated sexual function questionnaire was used to compare frequency of intercourse, libido, dyspareunia, orgasmic function, and vaginal dryness in women with and without prolapse (Weber, 1995). No differences were seen between the two groups. However, if a patient with POP describes an obstructing bulge as causing sexual dysfunction, therapy to reduce the bulge may be beneficial. Unfortunately, some prolapse procedures such as posterior repair with levator plication are believed to contribute to postoperative dyspareunia. Therefore, care should be taken in planning appropriate surgical procedures for women with concomitant sexual dysfunction.

PELVIC AND BACK PAIN

Many patients with pelvic organ prolapse complain of pelvic and low back pain, but there is little evidence to suggest a direct association. A cross-sectional study of 152 consecutive patients with POP did not find an association between pelvic or low back

pain and prolapse after controlling for age and prior surgery (Heit, 2002). Swift and colleagues (2003) found that back and pelvic pain were common among 477 women presenting for routine annual gynecologic examination and had no relationship to POP.

Some suggest that low back pain in a patient with prolapse may be caused by altered body mechanics. However, if pain is a primary symptom, other sources should be sought (see Chap. 11, Chronic Pain). In the absence of an identifiable etiology, temporary pessary placement is often beneficial to determine whether prolapse reduction will improve pain symptoms. Referral to a physical therapist may also shed light on a connection among prolapse, altered body mechanics, and pain.

ASYMPTOMATIC WOMEN

Many women with mild to advanced prolapse lack bothersome symptoms. Because the natural history of prolapse is unknown, it is difficult to predict if prolapse will worsen or if symptoms will develop. In this situation, benefits of treatment should be balanced against risk. Therefore, in the absence of other factors, invasive therapy is typically not selected for asymptomatic women. Pelvic floor muscle rehabilitation may be offered to a patient seeking to prevent prolapse progression. However, no data support the effectiveness of this practice (Adams, 2004; Hagen, 2004).

COMPARING SYMPTOMS TO DEGREE AND LOCATION OF PROLAPSE

Although POP has been associated with several different types of symptoms, the presence and severity of symptoms does not correlate well with advancing stages of prolapse. In addition, many common symptoms do not differentiate between compartments. Several studies have shown a poor predictive value among symptoms, the degree of their severity, and the degree of prolapse in a particular vaginal compartment (Ellerkmann, 2001; Jelovsek, 2005; Kahn, 2005; Weber, 1998). Thus, when planning surgical or nonsurgical therapy, realistic expectations should be set with regard to relief of symptoms. A patient should be informed that some symptoms cannot predictably be improved.

Physical Examination

Physical examination begins with a full body systems evaluation to identify pathology outside the pelvis. Systemic conditions such as cardiovascular, pulmonary, renal, or endocrinologic disease may affect treatment choices and should be identified early.

PERINEAL EXAMINATION

Initial pelvic examination is performed with a woman in lithotomy position. The vulva and perineum are examined for signs of vulvar or vaginal atrophy, lesions, or other abnormalities. A neurologic examination of sacral reflexes is performed using a cotton swab (see Chap. 23, General Inspection and Neurologic Evaluation). First, the *bulbocavernosus reflex* is elicited by tapping or stroking lateral to the clitoris and observing contraction of the bulbocavernosus bilaterally. Secondly, evaluation of anal sphincter innervation is completed by stroking lateral to the anus and observing a reflexive contraction of the anus, known as the *anal wink reflex* . The presence of these reflexes suggests normal sacral pathways. However, they may be absent in women who are neurologically intact, due to false-negative testing.

Pelvic organ prolapse examination begins by asking a woman to attempt Valsalva maneuver prior to placing a speculum in the vagina (Fig. 24-8). Patients who are unable to adequately complete a Valsalva maneuver are asked to cough. This "hands-off" approach more accurately displays true anatomy. With speculum examination, structures are artificially lifted, supported, or displaced. Importantly, this assessment helps answer three questions: (1) Does the protrusion come beyond the hymen?; (2) What is the presenting part of the prolapse (anterior, posterior, or apical)?; (3) Does the genital hiatus significantly widen with increased intra-abdominal pressure?

FIGURE 24-8

A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

C

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photographs of vaginal wall prolapse. **A.** Stage 2. This stage is defined by the most distal edge of the prolapse lying within 1 cm of the hymenal ring. **B.** Stage 3. This stage is defined by the most distal portion of the prolapse being >1 cm below the plane of the hymen, but protruding no farther than 2 cm less than the total vaginal length in centimeters. **C.** Stage 4. This stage is defined as complete or near complete eversion of the vaginal wall.

During examination, a clinician should verify that the full extent of the prolapse is being seen. Specifically, a woman should be asked to describe the extent of prolapse during real-life activities. This degree may be conveyed in terms of inches. Alternatively, a mirror may be placed at the perineum and visual confirmation can be obtained from the patient.

Prolapse is a dynamic condition that responds to the effects of gravity and intra-abdominal pressure. It frequently worsens over the course of a day or during physical activity. If the full extent of prolapse cannot be demonstrated, a woman should be examined in a standing position and during Valsalva maneuver.

VAGINAL EXAMINATION

If the POP-Q examination is performed, the genital hiatus (gh) and perineal body (pb) are measured during Valsalva maneuver (Fig. 24-9). The total vaginal length (TVL) is then measured by placing the marked ring forceps at the vaginal apex and noting the distance to the hymen. A bivalve speculum is then inserted to the vaginal apex. It displaces the anterior and posterior vaginal walls, and points C and D are then measured. The speculum is slowly withdrawn to assess descent of the apex. A split speculum is then used to displace the posterior vaginal wall and allow for visualization of the anterior wall and measurement of points Aa and Ba (Fig. 24-10). Attempts are made to characterize the nature of the anterior vaginal wall defect. Sagging lateral vaginal sulci with vaginal rugae still present suggest a *paravaginal defect* , that is, a lateral loss of support (Fig. 24-11B). A central bulge and loss of vaginal rugae is called a *midline* or *central defect* (see Fig. 24-6). If loss of support appears to arise from detachment of the anterior vaginal wall's apical segment from the apex, it is termed a *transverse defect* (Fig. 24-12). Transverse defects are assessed

by replacing the anterior apical segment and observing if the prolapse descends during Valsalva maneuver. The urethra is also evaluated during anterior vaginal wall assessment, and Q-tip testing can be performed to determine urethral hypermobility (see Fig. 23-8).

FIGURE 24-9

A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photograph displays clinical measurement of the genital hiatus (gh) and perineal body (pb). **A.** For POP-Q evaluation, a sponge stick is used that is marked at 1-, 2-, 3-, 4-, 5-, 7.5-, and 10-cm increments. Measurement is obtained with a woman performing maximum Valsalva maneuver. **B.** Measurement of the perineal body.

FIGURE 24-10

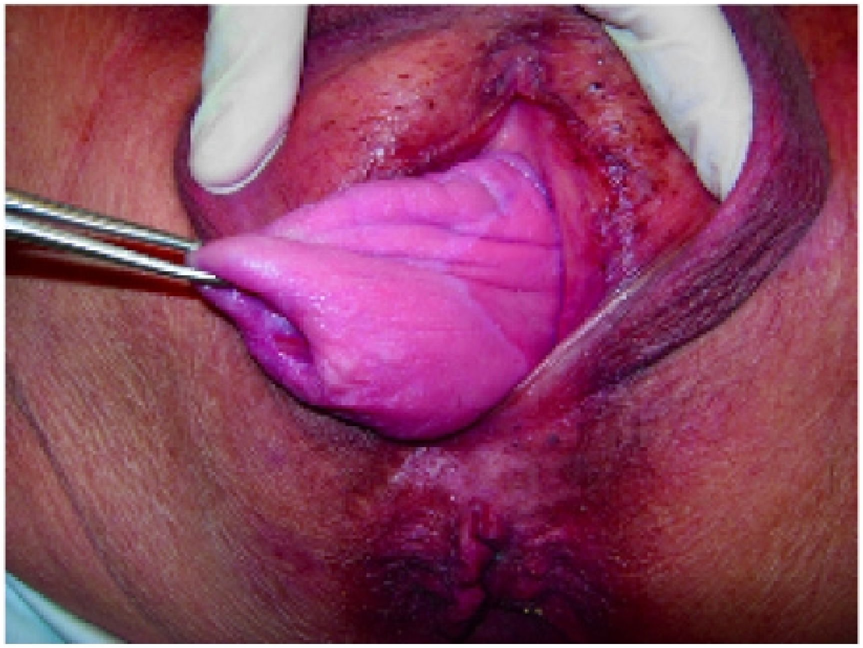
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photograph shows a split speculum displacing the posterior vaginal wall. This allows for measurement of points Aa and Ba. Aa is always defined as a discrete point lying 3 cm proximal to the urethral meatus and is measured in relation to the hymen. During measurement, downward traction should be avoided, as this causes artificial descent of the anterior vaginal wall.

FIGURE 24-11

A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

A. Photograph displays normal lateral support as noted by normal positioning of the vaginal sulci. **B.** Photograph reveals complete loss of lateral support, shown as absent lateral sulci.

FIGURE 24-12

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photograph displays a transverse vaginal wall defect. Note detachment of the anterior vaginal wall from the apex and the presence of rugae, which suggests that this is not a midline or central defect.

The split speculum is then rotated 180 degrees to displace the anterior wall and allow examination of the posterior wall. Points Ap and Bp are measured (Fig. 24-13). If the posterior vaginal wall descends, attempts are made to determine if rectocele or enterocele is present. Enterocele can only definitively be diagnosed by observing small bowel peristalsis behind the vaginal wall (Fig. 24-14). In general, bulges at the apical segment of the posterior vaginal wall should implicate enteroceles, whereas bulges in the distal posterior wall are presumed to be rectoceles. Further distinction may be found during standing rectovaginal examination. A clinician's index finger is placed in the rectum and thumb on the posterior vaginal wall. Small bowel may be palpated between the rectum and vagina, confirming enterocele.

FIGURE 24-13

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photograph showing a split speculum displacing the anterior vaginal wall. This allows for measurement of points Ap and Bp. Ap is always defined as a discrete point lying 3 cm proximal to the hymen.

FIGURE 24-14

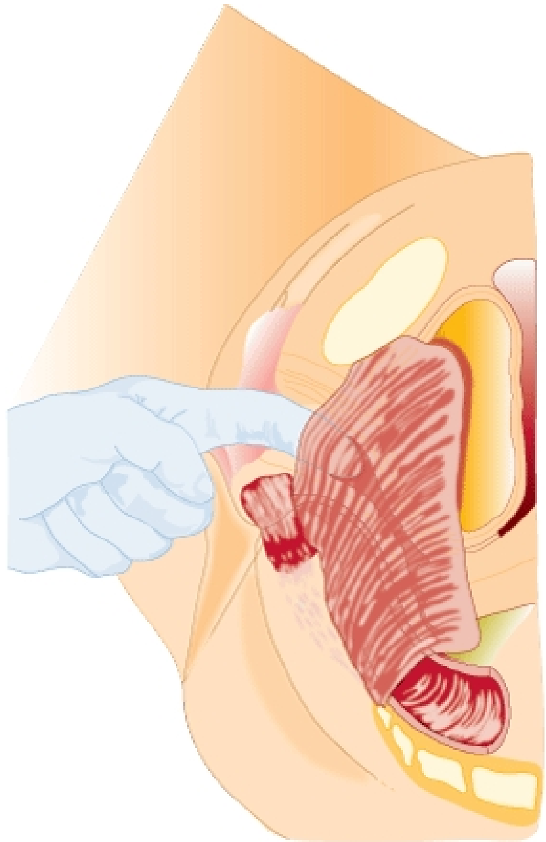
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photograph of enterocele. During evaluation, small bowel peristalsis may be noted behind the vaginal wall. Enterocele is most commonly noted at the vaginal apex, although anterior and posterior vaginal wall enteroceles may occur.

Overall, defect evaluation by vaginal examination has not been shown to have good inter- or intra-examiner reliability. However, individual evaluation may help assess prolapse severity and clarify anatomy if surgical correction is planned (Barber, 1999; Whiteside, 2004).

Bimanual examination is performed to identify other pelvic pathology. In addition, we strongly recommend assessment of pelvic floor musculature (Fig. 24-15). This examination is essential if pelvic floor rehabilitation is being considered as treatment. During evaluation, an index finger is placed 2 to 3 cm inside the hymen, at 4 and then 8 o'clock. Muscle resting tone and strength is assessed using the 0 through 5 Oxford grading scale. Five represents strong tone and strength (Laycock, 2002). Muscle symmetry is also evaluated. Asymmetric muscles, with palpable defects or scarring, may be associated with a prior obstetric forceps delivery or laceration.

FIGURE 24-15



Drawing depicts assessment of pelvic floor muscle assessment. The index finger is placed 2 to 3 cm inside the hymen at 4 and 8 o'clock. Both resting and contraction tone and strength are evaluated. *(From Toglia, 2003, with permission.)*

APPROACH TO TREATMENT

For women who are asymptomatic or mildly symptomatic, expectant management is appropriate. However, for women with significant prolapse or for those with bothersome symptoms, nonsurgical or surgical therapy may be selected. Treatment choice depends on the type and severity of symptoms, age and medical co-morbidities, desire for future sexual function and/or fertility, and risk factors for recurrence. Treatment should strive to provide symptom relief, but therapy benefits should always outweigh risks.

Often a combination of nonsurgical and surgical approaches may be selected. Symptoms should be ranked by severity and bother, and options for each should be discussed. An evidence-based appraisal of each option's success rate should be included. In the simplest case, a patient with prolapse of the vaginal apex beyond the hymen, whose only symptom is bulge or pelvic pressure, could be offered pessary or surgical treatment. In a more complicated case, a woman with prolapse beyond the hymenal ring may note a bulge, constipation, urge incontinence, and pelvic pain. Symptoms would be ranked as to severity of symptoms and importance of resolution. To address all complaints, therapy might involve pessary or surgery for bulge symptoms, as well as nonsurgical treatment of constipation, urge incontinence, and pelvic pain.

Nonsurgical Treatment

PESSARY USE IN PELVIC ORGAN PROLAPSE

Pessaries are the standard nonsurgical treatment for POP. Throughout history, various vaginal devices and materials for prolapse have been described, including cloth, wood, wax, metal, ivory, bone, sponge, and cork. Today's pessaries are usually made of silicone or inert plastic, and they are safe and simple to manage. Despite a long history of use, literature describing their indications, selection, and management is often anecdotal or contradictory.

Indications for Use

Pelvic organ prolapse is still the most common indication for vaginal pessary. Traditionally, pessaries have been reserved for women either unfit or unwilling to undergo surgery. A survey of the American Urogynecologic Society membership confirmed this sentiment among gynecologists with greater than 20 years in practice (Cundiff, 2000). However, the same survey showed that younger gynecologists, particularly those who described themselves as urogynecologists, used pessaries as a first-line therapy before recommending surgery. Women who have undergone at least one previous attempt at surgical management without relief may often choose a pessary over additional surgery.

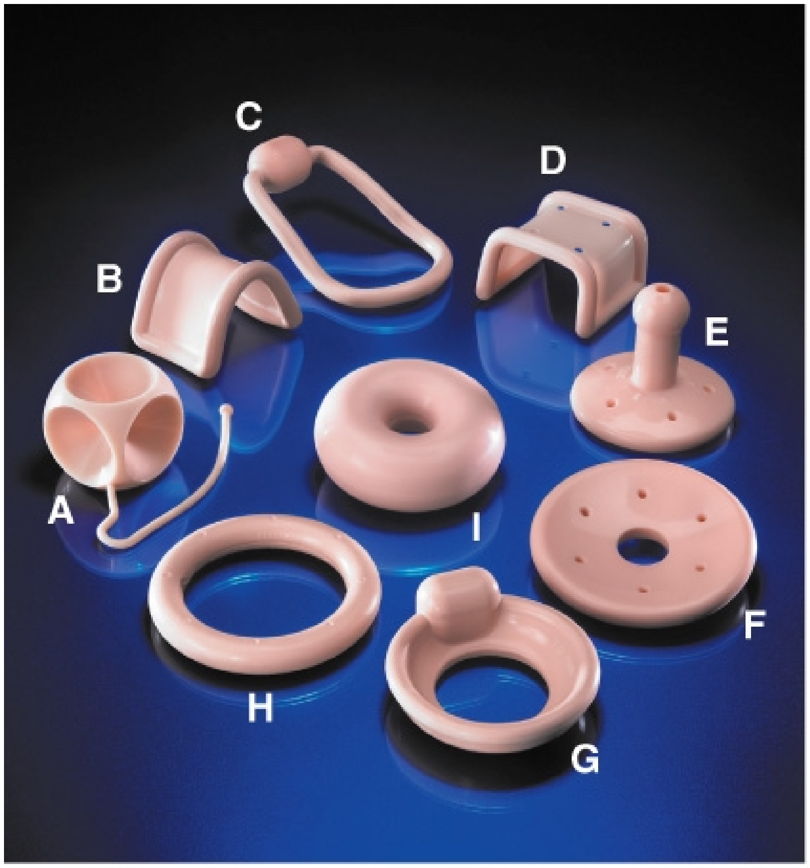
Pessaries may also be used diagnostically. As previously discussed, symptoms may not correlate with the type or severity of prolapse. Short-term pessary use may be helpful in this process. Even if a patient declines long-term pessary use, she may agree to a short trial to determine if her chief complaint is improved or resolved. A pessary may also be placed diagnostically to identify which women are at risk for urinary incontinence after prolapse-correcting surgery (Chaikin, 2000; Liang, 2004).

A recent multicenter randomized cross-over trial compared two pessary types for relief of prolapse symptoms and urinary complaints. This study demonstrated that pessaries provide a modest improvement in urinary obstructive, irritative, and stress symptoms (Schaffer, 2006) (see Chap. 23, Pessary and Urethral Inserts).

Types of Pessaries

Two broad categories of pessaries exist: support and space-filling pessaries (Fig. 24-16). Support pessaries, such as the ring pessary, use a spring mechanism that rests in the posterior fornix and against the posterior aspect of the symphysis pubis. Vaginal support results from elevation of the superior vagina by the spring, which is supported by the symphysis pubis. Ring pessaries may be constructed as a simple circular ring or as a ring with support that looks like a large contraceptive diaphragm (Fig. 24-17). These are effective in women with first- and second-degree prolapse, and the support ring's diaphragm is especially useful in women with accompanying anterior vaginal wall prolapse. When properly fitted, the device should lie behind the pubic symphysis anteriorly and behind the cervix posteriorly.

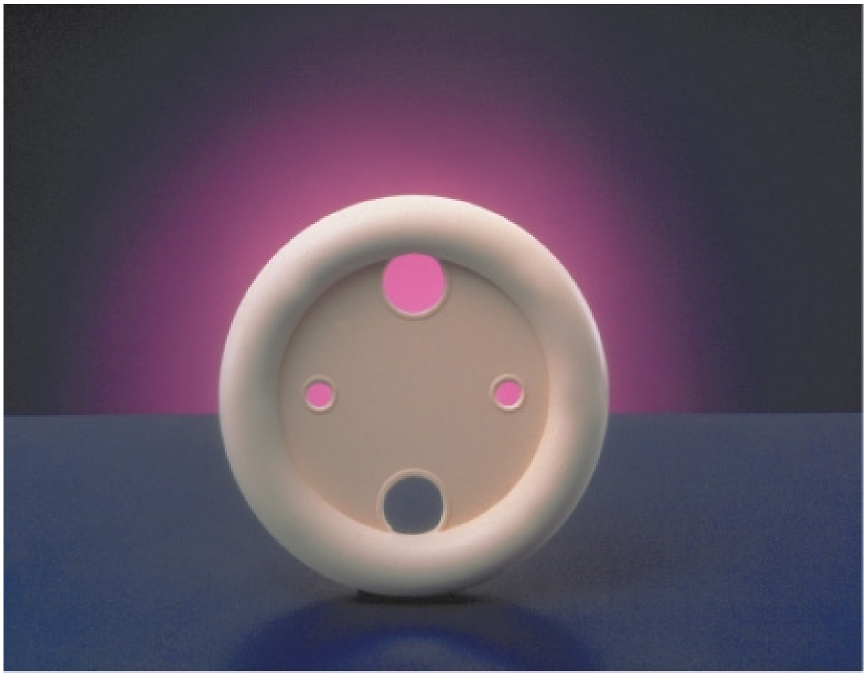
FIGURE 24-16



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photograph displays types of pessaries. **A.** Cube pessary. **B.** Gehrung pessary. **C.** Hodge with knob pessary. **D.** Regula pessary. **E.** Gellhorn pessary. **F.** Shaatz pessary. **G.** Incontinence dish pessary. **H.** Ring pessary. **I.** Donut pessary. *(Courtesy of Milex, Cooper Surgical.)*

FIGURE 24-17



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Ring pessary with support. *(Courtesy of Milex, Cooper Surgical.)*

In contrast, space-filling pessaries maintain their position by creating suction between the pessary and vaginal walls (cube), by creating a diameter larger than the genital hiatus (donut), or by both mechanisms (Gellhorn). The Gellhorn is often used for moderate to severe prolapse and for complete procidentia (Fig. 24-18). It contains a concave disk that fits against the cervix or vaginal cuff and has a stem that is positioned just cephalad to the introitus. The concave disk supports the vaginal apex by creating suction, and the stem is useful for device removal. Of all pessaries, the two most commonly used and studied devices are the ring and Gellhorn pessaries.

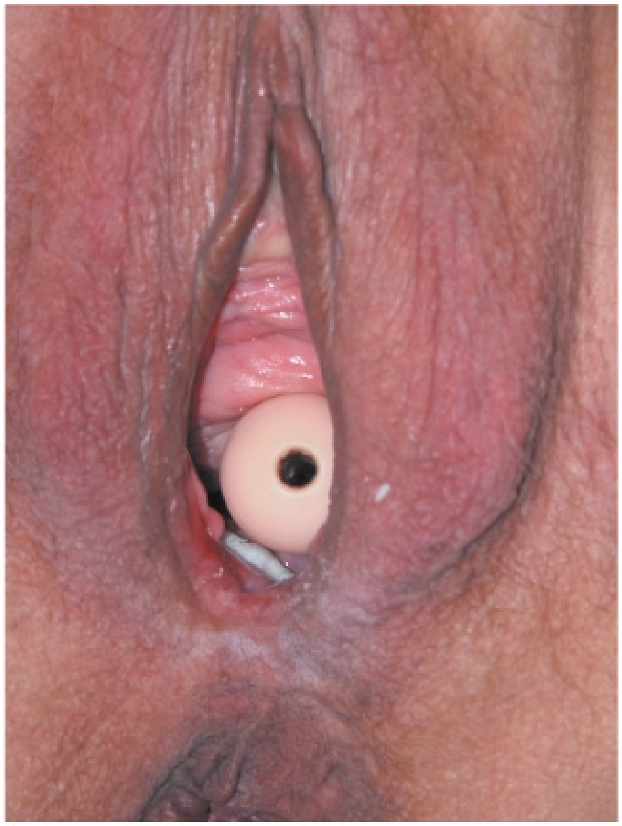
FIGURE 24-18

A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

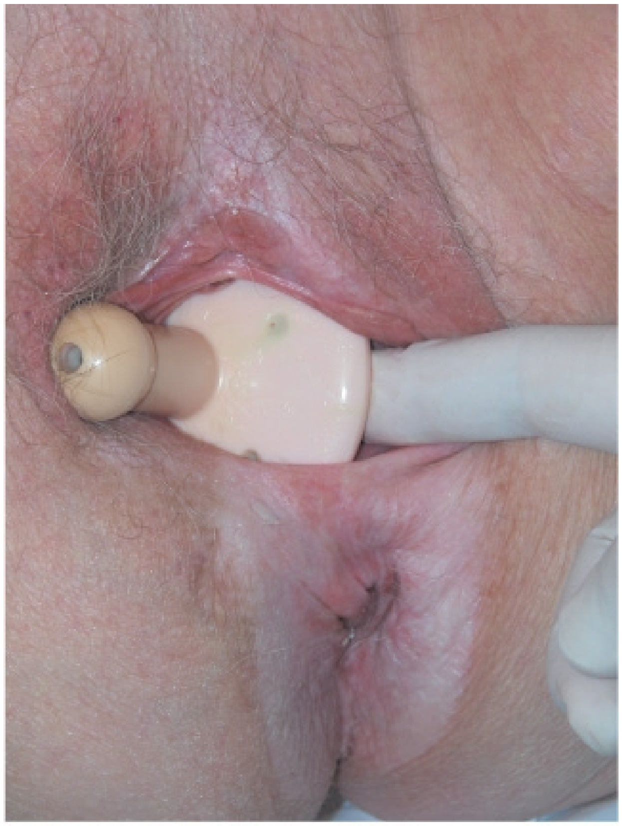
B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



C

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



D

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photographs display technique for placement and removal of a Gellhorn pessary. Figures **A, B,** and **C** show placement. **D.** To remove a Gellhorn pessary, an index finger is placed behind the disk and suction is broken prior to removal.

Patient Evaluation and Pessary Placement

A patient must be an active participant in the treatment decision to use a pessary. Its success will depend upon her ability to care for the pessaryâ€”either alone or with the assistance of a caretakerâ€—and her willingness and availability to come for subsequent evaluations. Vaginal atrophy should be treated before or concomitantly with pessary initiation. The type of device selected may be affected by patient factors such as hormonal status, sexual activity, prior hysterectomy, and stage and site of POP. After a pessary is selected, a woman should be fitted with the largest size that can be comfortably worn. If a pessary is ideally fitted, a patient is not aware of its presence. As a woman ages and gains or loses weight, alternate sizes may be required.

Generally, a patient is fitted with a pessary while in the lithotomy position after she has emptied both her bladder and rectum. A digital examination is performed to assess vaginal length and width, and an initial estimation of pessary size is made. To introduce a ring pessary, the device is held in the clinician's dominant hand in a folded position (Fig. 24-18). Lubricant is placed on either the vaginal introitus or the pessary's leading edge. While holding the labia apart, the pessary is inserted by pushing in an inferior, cephalad direction against the posterior vaginal wall. Next, an index finger is directed into the posterior vaginal fornix to ensure that the cervix is resting above the pessary. The clinician's finger should barely slide between the lateral edges of the ring pessary and the vaginal sidewall.

Following pessary placement, a woman is prompted to perform a Valsalva maneuver, which might dislodge an improperly fitted pessary. She should be able to stand, walk, cough, and urinate without difficulty or discomfort. Instruction on removal and placement should then follow. For removal of a ring pessary, an index finger is inserted into the vagina to hook the ring's leading

edge. Traction is applied along the vaginal axis to bring the ring toward the introitus. Here it may be grasped by the thumb and index finger and removed.

Ideally, a pessary is removed nightly to weekly, washed in soap and water, and replaced the next morning. Women are sent home from their initial fitting session with instructions describing the management of commonly encountered problems (Table 24-7). After initial placement, a return visit may follow in 1 to 2 weeks. For patients comfortable with their pessary management, return visits may be semiannual. For those unable or unwilling to remove and replace a device themselves, a pessary may be removed and the patient's vagina inspected at the provider's office every 3 months. Scheduling of subsequent visits is individualized.

Table 24-7 Guidelines for Pessary Care

Pessary type__________
Size__________

1. After your initial pessary fitting is successful, you will be asked to return for a follow-up appointment in about 2 weeks. The purpose of this visit is to check the pessary and examine the vagina to ensure that it is healthy. Follow-up appointments will follow this schedule:
   1st year: every 3–6 months
   2nd year and beyond: every 6 months
   You may learn to care for the pessary yourself. For those patients who can remove and insert the pessary themselves, we recommend weekly overnight removal and cleansing of the pessary with soap and warm water. These patients should see the doctor at least once per year.
2. The following is a list of problems you may encounter with the pessary and our recommendations for their management.

Problem	Management
A. The pessary falls out.	Keep the pessary and notify your doctor's office. An appointment will be made. It may be possible that a change in the size or the type of pessary is needed.
B. You experience pelvic pain.	Notify your doctor's office. If the pessary has slipped and you can remove it, do so. Otherwise, have your doctor remove the pessary. A change in pessary size or type may be needed.
C. Vaginal discharge and odor.	You can douche with warm water and you may want to try using Trimo-San vaginal gel 1–3 times a week.
D. Vaginal bleeding.	Vaginal bleeding may be a sign that the pessary is irritating the lining of the vagina. Call your doctor's office and arrange an appointment.
E. Leaking from the bladder.	Sometimes, the support provided by the pessary will cause leaking from the bladder. Notify your doctor and discuss this problem.

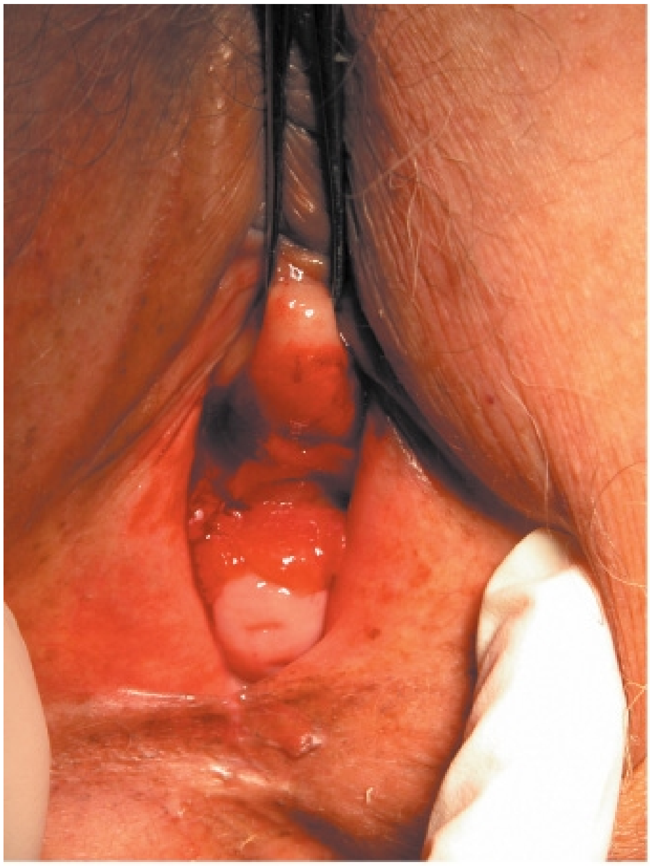
Trimo-San (Oxyquinolone, Milex Products, Chicago, IL) helps restore and maintain the normal vaginal acidity that helps reduce odor-causing bacteria.s

From Farrell, 1997, with permission.

Complications with Pessary Use

Serious complications such as erosions into adjacent organs are rare with proper use and usually result only after years of neglect. At each return visit, the pessary is removed and the vagina is inspected for erosions, abrasions, ulcerations, or granulation tissue (Fig. 24-19). Vaginal bleeding is usually an early sign and should not be ignored. *Pessary ulcers* or abrasions are treated by changing the pessary type or size to alleviate pressure points or by removing the pessary completely until healing occurs. *Prolapse ulcers* have the same appearance as pessary ulcers, however, they result from the prolapsed bulge rubbing on a patient's clothes. These are treated by placing a pessary. Treatment of vaginal atrophy with local or systemic estrogen is commonly required. Alternatively, water-based lubricants applied to the pessary may help prevent these complications.

FIGURE 24-19



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photograph shows granulation tissue involving the anterior and posterior vaginal wall resulting from pessary trauma.

Pelvic pain with pessary use is not normal. This usually indicates that the size is too large and is an indication for substituting a smaller-sized pessary. All pessaries tend to trap vaginal secretions and obstruct normal drainage to some degree. The resultant odor may be managed by encouraging more frequent nighttime device removal, washing, and re-insertion the next day. Alternatively, a woman may use Trimo-San gel (Milex Products, Chicago, IL) once or twice weekly or may douche with warm water. Trimo-San gel helps restore and maintain normal vaginal acidity that aids in reducing odor-causing bacteria.

PELVIC FLOOR MUSCLE EXERCISE

Pelvic floor muscle exercise has been suggested as a therapy that might limit progression and alleviate prolapse symptoms. Also known as Kegel exercises, these muscle-strengthening techniques are described in Chapter 23, Pelvic Floor Strengthening Exercises. There are two hypotheses that describe the benefits of pelvic floor muscle exercise for prolapse prevention and treatment (BÃ¸, 2004). First, from these exercises, women learn to consciously contract muscles before and during increases in abdominal pressure, which prevents organ descent. Alternatively, regular muscle strength training builds permanent muscle volume and structural support.

Unfortunately, there is no high-quality scientific evidence supporting pelvic exercise for prevention and treatment of prolapse (Hagen, 2004). However, pelvic floor exercise has minimal risk and low cost. For this reason, it may be offered to asymptomatic or mildly symptomatic women who are interested in prevention of progression and who decline other treatments.

SURGICAL TREATMENT

Obliterative Procedures

The two approaches to prolapse surgery are obliterative and reconstructive. The obliterative approach includes Lefort colpocleisis and complete colpocleisis (see Sections 42-23, Lefort Partial Colpocleisis and 42-24, Complete Colpocleisis). These procedures involve removing extensive vaginal epithelium, suturing anterior and posterior vaginal walls together, obliterating the vaginal vault, and effectively closing the vagina. Obliterative procedures are only appropriate for elderly or medically compromised patients, who have no future desire for coital activity.

Obliterative procedures are technically easier, require less operative time, and offer superior success rates compared with reconstructive procedures. Success rates for colpocleisis range from 91 to 100 percent, although the quality of evidence-based studies supporting these rates is poor (FitzGerald, 2006). Less than 10 percent of patients express regret after colpocleisis, often due to loss of coital activity (FitzGerald, 2006; Wheeler, 2005). Latent stress urinary incontinence can be unmasked with colpocleisis due to downward traction on the urethra.

Reconstructive Procedures

These surgeries attempt to restore normal pelvic anatomy and are more commonly performed than obliterative procedures for POP. Vaginal, abdominal, and laparoscopic approaches may be used and selection is individualized. However, in the United States, a vaginal approach is preferred by most for prolapse repair (Boyles, 2003; Brown, 2002; Brubaker, 2005a; Olsen, 1997).

The decision to proceed with a vaginal or abdominal approach depends on multiple factors including the patient's unique characteristics and surgeon's expertise. In certain instances, an abdominal approach appears to have clear advantages (Benson, 1996; Maher, 2004a, 2004b). These include women with prior failure of a vaginal approach, a shortened vagina, or those believed to be at higher risk for recurrence, such as young women with severe prolapse. In contrast, a vaginal approach typically offers shorter operative time and a quicker return to daily activities.

LAPAROSCOPY

A laparoscopic approach to prolapse is currently being used by experienced laparoscopic surgeons. Procedures include sacrocolpopexy, uterosacral ligament vaginal vault suspension, paravaginal repair, enterocele repair, and rectocele repair. In addition, robotic laparoscopic sacrocolpopexy is currently performed in centers with the da Vinci Robot (Intuitive Surgical, Sunnyvale, CA), and this has potential to decrease operative time.

Outcome studies of laparoscopic pelvic reconstruction, however, are mostly limited to case series (Higgs, 2005). Comparing laparoscopic and open approaches without randomized trials is difficult. However, surgeons with advanced laparoscopic skills who can perform the same operation laparoscopically should have equivalent results.

SURGICAL PLAN

Reconstructive prolapse repair will often involve a combination of procedures in several vaginal compartments. However, the decision regarding which compartments to repair is not always straightforward. In the past, a defect-directed approach to prolapse repair was preferred. With this approach, it was believed that all current, latent, or potential compensatory defects should be evaluated and repaired. However, current expert opinion suggests that asymptomatic areas of prolapse do not always warrant repair, and in fact, correction can lead to de novo symptoms. For instance, repair of an asymptomatic posterior wall prolapse may lead to dyspareunia. Thus, surgery should be designed to relieve *current* symptoms.

ANTERIOR COMPARTMENT

Many procedures for anterior vaginal wall prolapse repair have been described. Historically, anterior colporrhaphy has been the most common operation, yet long-term success rates are poor. In a randomized trial of three anterior colporrhaphy techniques (traditional midline plication, ultralateral repair, and traditional plication plus lateral reinforcement with synthetic mesh), Weber and colleagues (2001b) found a low rate of anatomic success. Satisfactory anatomic results were obtained in only 30 percent of the traditional group, 46 percent of the ultralateral group, and 42 percent of the traditional plus mesh group. These differences were not statistically significant. Although still frequently performed, the poor rates of anatomic success with traditional anterior

colporrhaphy have prompted re-evaluation of repair concepts and development of other procedures.

Despite these limitations, if a central or midline defect is suspected, anterior colporrhaphy may be performed (see Section 42-13, Anterior Colporrhaphy). Mesh or biomaterial may also be used in conjunction with anterior colporrhaphy or by itself. The mesh is used to reinforce the vaginal wall and is sutured in place laterally. However, the use of mesh and mesh kits for anterior vaginal wall prolapse has not been well studied and should be considered experimental (American College of Obstetricians and Gynecologists, 2007).

In many cases, anterior vaginal wall prolapse results from fibromuscular defects at the anterior apical segment or transverse detachment of the anterior apical segment from the vaginal apex. In these situations, an apical suspension procedure such as an abdominal sacrocolpopexy or uterosacral ligament vaginal vault suspension will resuspend the anterior vaginal wall to the apex and reduce anterior wall prolapse (see Sections 42-17, Abdominal Sacrocolpopexy and 42-18, Abdominal Uterosacral Ligament Suspension). Continuity is also re-established between the anterior and posterior vaginal fibromuscular layers to prevent enterocele formation.

Alternatively, if a lateral defect is suspected, paravaginal repair can be performed through the vaginal, abdominal, or laparoscopic route (see Section 42-14, Abdominal Paravaginal Defect Repair). Paravaginal repair is performed by re-attaching the fibromuscular layer of the vaginal wall to the arcus tendineus fascia pelvis.

VAGINAL APEX

There is a growing appreciation that support of the vaginal apex provides the cornerstone for a successful prolapse repair. Some experts believe that isolated surgical repair of the anterior and posterior walls is doomed for failure if the apex is not adequately supported (Brubaker, 2005b).

The vaginal apex can be resuspended with a number of procedures including abdominal sacrocolpopexy, sacrospinous ligament fixation, or uterosacral ligament vaginal vault suspension.

Abdominal Sacrocolpopexy

This surgery suspends the vaginal vault to the sacrum using synthetic mesh. Primary advantages include durability and conservation of normal vaginal anatomy. For example, compared with other vault suspension procedures, abdominal sacrocolpopexy offers greater vaginal apex mobility and avoids vaginal shortening. In addition, abdominal sacrocolpopexy provides enduring correction of apical prolapse, and long-term success rates approximate 90 percent. This procedure may be used primarily or as a second surgery for women with recurrences after failure of otherprolapse repairs.

Sacrospinous Ligament Fixation

This is one of the most popular procedures for apical suspension. The vaginal apex is suspended to the sacrospinous ligament unilaterally or bilaterally using a vaginal extraperitoneal approach. After SSLF, recurrent apical prolapse is uncommon, however, anterior vaginal wall prolapse develops postoperatively in 6 to 28 percent of patients (Benson, 1996; Morley, 1988; Paraiso, 1996). Complications associated with sacrospinous ligament fixation (SSLF) include buttock pain in 3 percent of patients and vascular injury in, 1 percent (Sze, 1997a, 1997b). Although uncommon, significant and life-threatening hemorrhage can follow injury to blood vessels located behind the sacrospinous ligament (see Section 42-20, Sacrospinous Ligament Fixation).

Uterosacral Ligament Vaginal Vault Suspension

With this procedure, the vaginal apex is attached to remnants of the uterosacral ligament at the level of the ischial spines or higher (see Section 42-19, Vaginal Uterosacral Ligament Suspension). Performed vaginally or abdominally, the uterosacral ligament vaginal vault suspension is believed to replace the vaginal apex to a more anatomic position than SSLF, which deflects the vagina posteriorly (Barber, 2000; Maher, 2004b; Shull, 2000).

This procedure has been adopted by many surgeons in the United States in attempts to reduce the rates of anterior vaginal prolapse recurrence following SSLF (Shull, 2000). Although uterosacral ligament vaginal vault suspension has gained wide popularity, studies supporting its use are limited to retrospective case series (Amundsen, 2003; Karram, 2001; Silva, 2006). In these studies and others, anterior vaginal prolapse recurrence rates range from 1 to 7 percent, and overall recurrence, from 4 to 18

percent.

HYSTERECTOMY AT THE TIME OF PROLAPSE REPAIR

In the United States, hysterectomy is often performed concurrently with prolapse surgery. Conversely, in many European countries, it is rarely performed during pelvic floor reconstruction. Although arguments exist for both, comparison has not been performed in randomized prospective trials.

If apical or uterine prolapse is present, hysterectomy will more readily allow the vaginal apex to be resuspended with the previously described apical suspension procedures. If hysterectomy is not performed in the context of apical prolapse, these procedures must be modified or specific uterine suspension procedures performed (not described in this text). Alternatively, if apical or cervical prolapse is not present, hysterectomy need not be incorporated into prolapse repair.

POSTERIOR COMPARTMENT

Enterocele Repair

Posterior vaginal wall prolapse may be due to enterocele or rectocele. Enterocele is defined as herniation of the small bowel through the vaginal fibromuscular layer, usually at the vaginal apex. Discontinuity of the anterior or posterior vaginal wall fibromuscular layers allows for this herniation. Accordingly, enterocele repairs have as their goal re-attachment of the fibromuscular layers. If posterior wall prolapse is due to enterocele, repair of this defect should reduce the posterior wall prolapse.

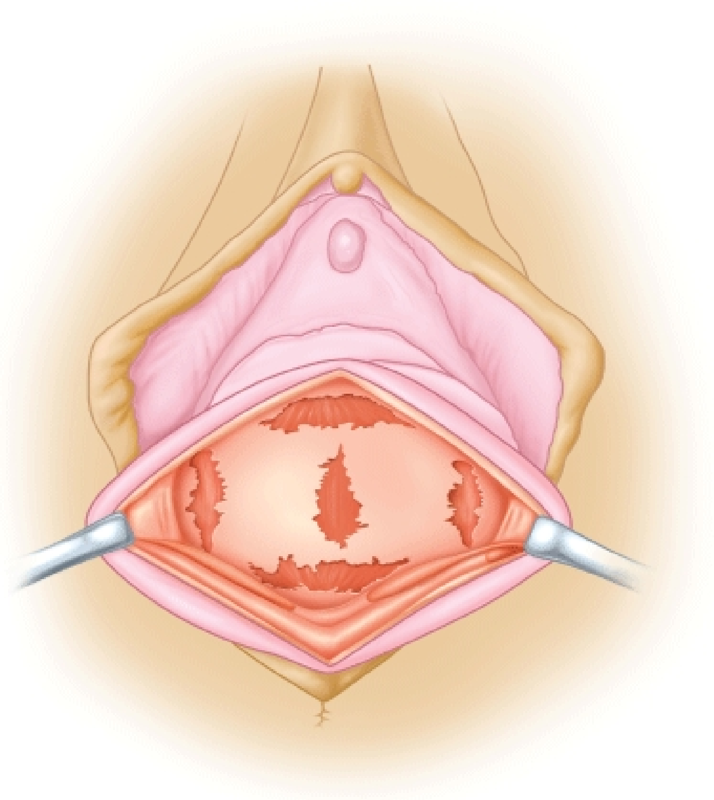
Rectocele Repair

Posterior vaginal wall prolapse due to rectocele is repaired with one of several techniques. Traditional posterior colporrhaphy aims to rebuild the fibromuscular layer between the rectum and vagina by performing a midline fibromuscular plication (see Section 42-15, Posterior Colporrhaphy). The anatomic cure rate is 76 to 96 percent, and most studies report a greater than 75-percent improvement rate of bulge symptoms (Cundiff, 2004). To narrow the genital hiatus and prevent recurrence, some surgeons plicate the levator ani muscles concurrently with posterior repair. However, this practice may contribute to dyspareunia rates of 12 to 27 percent (Kahn, 1997; Mellegren, 1995; Weber, 2000). Thus, it is best avoided in women who are sexually active.

Site-Specific Posterior Repair

This approach to posterior vaginal wall prolapse was first described by Richardson in 1993. This repair is based on the assumption that specific tears exist in the fibromuscular layer, which can be identified and repaired in a discrete fashion (see Section 42-15, Posterior Colporrhaphy). Defects may be midline, lateral, distal, or superior (Fig. 24-20). This approach is conceptually analogous to a fascial hernia, in which the fascial tear is identified and repaired. Thus, its theoretical advantage lies in its restoration of normal anatomy rather than plication of tissue in the midline.

FIGURE 24-20



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Drawing depicts posterior vaginal wall defects. These may be midline, lateral, distal, or apical. (*From Richardson, 1993, with permission.*)

Site-specific repair has gained wide acceptance, however, anatomic cure rates range from 56 to 100 percent, similar to that with traditional posterior colporrhaphy (Muir, 2007). Moreover, anatomic and functional long-term outcomes are not known.

Mesh Reinforcement

In an effort to reduce prolapse recurrence, graft augmentation with allograft, xenograft, or synthetic mesh, has been used in conjunction with posterior colporrhaphy and site-specific repair. Generally, the graft is placed after colporrhaphy or site-specific repair is completed. Moreover, in situations in which the fibromuscular layer cannot be identified to perform a midline plication or site-specific repair, graft augmentation may be the only surgical option.

Mesh is sutured in place laterally with a minimum number of sutures. If technically possible, the graft is attached to the vaginal apex and the uterosacral ligament. Distally, the graft is attached to the perineal body.

The efficacy and safety of graft augmentation in the posterior vaginal wall has not been established. Paraiso and co-workers (2006) randomized 105 women to posterior colporrhaphy, site-specific repair, or site-specific repair plus porcine small intestine submucosa graft. After 1 year, those with graft augmentation had a significantly higher anatomic failure rate (46 percent) than those who received site-specific repair alone (22 percent) or posterior colporrhaphy (14 percent). More research is needed to determine the safety, efficacy, and optimal material for posterior wall graft augmentation.

Sacrocolpoperineopexy

This modification of sacrocolpopexy may be selected for correction of posterior vaginal wall descent when an abdominal approach is employed for other prolapse procedures or if treatment of perineal descent is necessary (Cundiff, 1997; Lyons, 1997; Sullivan,

2001; Visco, 2001). With this procedure, the posterior sacrocolpopexy mesh is extended down the posterior vaginal wall to the perineal body (see Fig. 42-15.11). In several case series, anatomic cure rates were greater than 75 percent.

PERINEUM

The perineum provides distal support to the posterior vaginal wall and anterior rectal wall and anchors these structures to the pelvic floor. A disrupted perineal body will allow descent of the distal vagina and rectum and will contribute to a widened levator hiatus.

Perineorrhaphy is often done in conjunction with posterior repair to recreate normal anatomy (see Section 42-16, Perineorrhaphy). During surgery, the perineum is rebuilt through midline plication of the perineal muscles and connective tissue. Importantly, overly aggressive plication can narrow the introitus, create a posterior vaginal wall ridge, and lead to entry dyspareunia. However, in a woman who is not sexually active, high perineorrhaphy with intentional introital narrowing is believed to decrease the risk of posterior wall prolapse recurrence.

THE USE OF MESH AND MATERIALS IN RECONSTRUCTIVE PELVIC SURGERY

Mesh Indications

Approximately 30 percent of women undergoing surgery for prolapse will require a repeat operation for recurrence (Olsen, 1997). As such, there is a continuous effort to improve surgical procedures and outcomes.

Synthetic mesh for sacrocolpopexy and midurethral slings has been widely studied and is safe and effective. Mesh erosion occurs in a small percentage of cases, but can be managed with local estrogen therapy and limited vaginal excision. Rarely is excision of the entire mesh warranted. In an attempt to limit erosion rates, surgeons have used biologic material, including cadaveric fascia. However, high rates of prolapse recurrence are associated with this material (FitzGerald, 1999, 2004; Gregory, 2005). Therefore, synthetic mesh is recommended.

The use of biologic or synthetic grafts for other transvaginal reconstructive pelvic surgery has expanded rapidly in the absence of supporting long-term safety and efficacy data. Some surgeons routinely use graft augmentation, others never use it, and some use it only for limited indications. Selective use may include: (1) the need to bridge a space, (2) weak or absent connective tissue, (3) connective tissue disease, (4) high risk for recurrence (obesity, chronically increased intra-abdominal pressure, and young age), and (5) shortened vagina. High-quality scientific data are lacking to support the use of grafts for augmentation of transvaginal prolapse repairs. Accordingly, the American College of Obstetricians and Gynecologists (2007) considers this practice experimental, and women should consent to surgery with this understanding.

Mesh Material

Surgeons using grafts should be familiar with the different types and their characteristics. Biologic grafts may be autologous, allograft, or xenograft. *Autologous* grafts are harvested from another part of the body such as rectus abdominis fascia or fascia lata. Morbidity is low, but may include increased operative time, pain, hematoma, or weakened fascia at the harvest site. *Allografts* come from a human source other than the patient and include cadaveric fascia or cadaveric dermis. *Xenografts* are biologic tissue obtained from a source or species foreign to the patient such as porcine dermis, porcine small intestinal submucosa, or bovine pericardium. Biologic materials have varying biomechanical properties and, as noted earlier, are associated with high rates of prolapse recurrence. Thus, recommendations on the appropriate clinical situations for biologic material are limited.

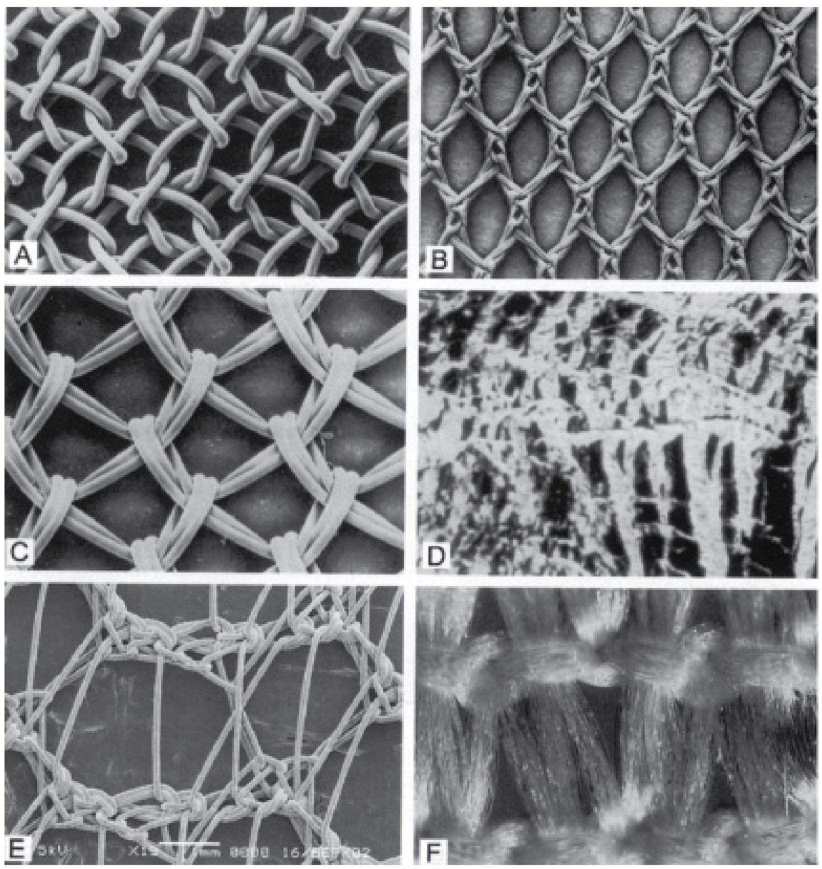
Synthetic grafts are classified as types I to IV, based on pore size (Table 24-8 and Fig. 24-21) (Amid, 1997). Pore size is the most important property of synthetic mesh. Bacteria generally measure less than 1 μm, whereas granulocytes and macrophages are typically larger than 10 μm. Thus, a mesh with pore size <10 μm may allow bacterial but not macrophage infiltration, and predispose to infection. Accordingly, type I mesh has the lowest rate of infection compared with types II and III. Pore size is also the basis of tissue ingrowth, angiogenesis, flexibility, and strength. Pore sizes of 50 to 200 μm allow for superior tissue ingrowth and collagen infiltration, again favoring type I. Meshes are either monofilament or multifilament. Multifilament mesh has small intrafiber pores that can harbor bacteria, therefore, monofilament mesh is recommended. From these findings, consensus suggests that if synthetic mesh is used, type I monofilament is the best choice for reconstructive pelvic surgery.

Table 24-8 Types of Surgical Mesh.

Type I:	Macroporous. Pore size >75 µm (size required for infiltration by macrophages, fibroblasts, blood vessels in angiogenesis, and collagen fibers) *GyneMesh, Atrium, Marlex, Prolene*
Type II:	Microporous. Pore size <10 µm in at least 1 dimension *Gore-Tex*
Type III:	Macroporous patch w/multifilaments or a microporous component *Teflon, Mersilene, Surgipro, Mycro Mesh*
Type IV:	Submicronic. Pore size <1 µm. Often used in association with type I mesh for intraperitoneal adhesion prevention *Silastic, Cellgard, Preclude*

Compiled from Amid, 1997.

FIGURE 24-21



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photograph depicts different types of surgical mesh. **A.** Marlex. **B.** Mersilene. **C.** Prolene. **D.** Gore-Tex. **E.** Gynemesh-PS. **F.** IVS (intravaginal slingplasty) mesh. (*From Iglesia, 1997, with permission.*)

Graft augmentation will undoubtedly persist due to the current poor cure rates with traditional transvaginal repairs. However, there is presently a paucity of evidence to guide the surgeon and provide a patient with accurate safety and efficacy information.

Moreover, industry-driven, premature adoption of untested materials and procedures has historically led to unacceptable complications. For these reasons, randomized, prospective trials comparing traditional repairs with graft augmentation are urgently needed.

Concomitant Prolapse and Incontinence Surgery

Prior to prolapse surgery, women should be evaluated for stress urinary incontinence (SUI) (see Chap. 23, Symptom Clustering). Those with bothersome SUI symptoms should be considered for concurrent anti-incontinence surgery. However, in women without SUI symptoms, latent stress incontinence may be unmasked or SUI may develop de novo following prolapse repair. Therefore, preoperative urodynamic testing with the prolapse replaced is recommended. If stress incontinence is demonstrated, these patients also should be considered for a concurrent anti-incontinence operation. This has been a difficult decision for patients and surgeons because a procedure with known risks is being performed for a problem that does not currently exist and may never develop. However, the recent CARE (Colpopexy and Urinary Reduction Efforts) trial has shed new light on this problem (Brubaker, 2006). Women undergoing abdominal sacrocolpopexy for prolapse (anterior vaginal wall stage 2 or greater) who did not exhibit symptoms of stress incontinence were randomized to undergo concurrent Burch colposuspension or not. Preoperative urodynamic testing was performed but surgeons were blinded to the results. Three months after surgery, 24 percent of women in the Burch group and 44 percent of women in the control group met one or more criteria for stress incontinence. The incontinence was bothersome in 6 percent of the Burch group and 24 percent of the control group.

These data can be interpreted in several ways. It can be argued that all women undergoing sacrocolpopexy for stage 2 or greater anterior vaginal wall prolapse should undergo Burch colposuspension, as 44 percent will develop stress incontinence symptoms. However, the opposing argument is that only 24 percent will develop bothersome incontinence symptoms, thus three quarters of women would be subjected to an unnecessary operation.

Importantly, this study provides Level 1 evidence for a surgeon to share during patient counseling. The authors of this study caution that these data cannot be extrapolated to other prolapse and incontinence surgeries. However, in lieu of other Level 1 evidence, surgeons can still use this information in surgical planning and presurgical patient discussions.

CONCLUSION

Pelvic organ prolapse is a significant health concern for women. Evaluation should focus on symptoms, their anatomic correlation, and their effect on patient quality of life. Nonsurgical and surgical therapy should be symptom-based and should be undertaken with a realistic, evidence-based assessment of outcomes.

Current research is focused on improving treatment outcomes. In the future, a greater knowledge of modifiable risk factors such as events surrounding pregnancy and delivery, may allow improved opportunities for prevention.

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ANAL INCONTINENCE

Anal incontinence (AI) is an involuntary loss of flatus, liquid, or solid stool that causes a social or hygienic problem (Abrams, 2005). This condition may lead to poor self-image and social isolation, thus significantly impairing quality of life (Johanson, 1996; Perry, 2002). Additionally, AI creates a substantial financial burden to patients and the health care system (Whitehead, 2001).

The definition of AI includes incontinence of flatus, whereas that of *fecal incontinence* (FI) does not. Not included in either definition is *anal mucoid seepage* . This type of fecal leakage develops in those with a fully functional anal sphincter and intact cognition. It most often is associated with organic colonic disease or dietary sensitivity (Abrams, 2005).

Epidemiology

Anal incontinence is common and affects all age groups. In contrast to previous beliefs, it affects men and women similarly (Madoff, 2004; Nelson, 2004). In a recent systematic review of the literature, Macmillan and co-workers (2004) reported that the estimated prevalence of AI among community-dwelling adults ranges between 2 and 24 percent if flatal incontinence is included, and between 0.4 and 18 percent if flatal incontinence is not (Macmillan, 2004). Wide variations are attributed to differences in definition, lack of validated tools, and surveyed cohort's age. In a multicenter trial that included seven geographically distinct sites in the United States, Boreham and co-workers (2005) reported the prevalence, risk factors, and impact upon quality of life of AI in women aged 18 to 65 years presenting for benign gynecologic care. The overall prevalence of AI in this cohort was 28 percent. The prevalence of AI increases with age, and has been reported to reach 46 percent in older, institutionalized women (Nelson, 1998).

Pathophysiology of Defecation and Anal Continence

Normal defecation and anal continence are complex processes that require a competent anal sphincter complex, normal anorectal sensation, adequate rectal capacity and compliance, and conscious control.

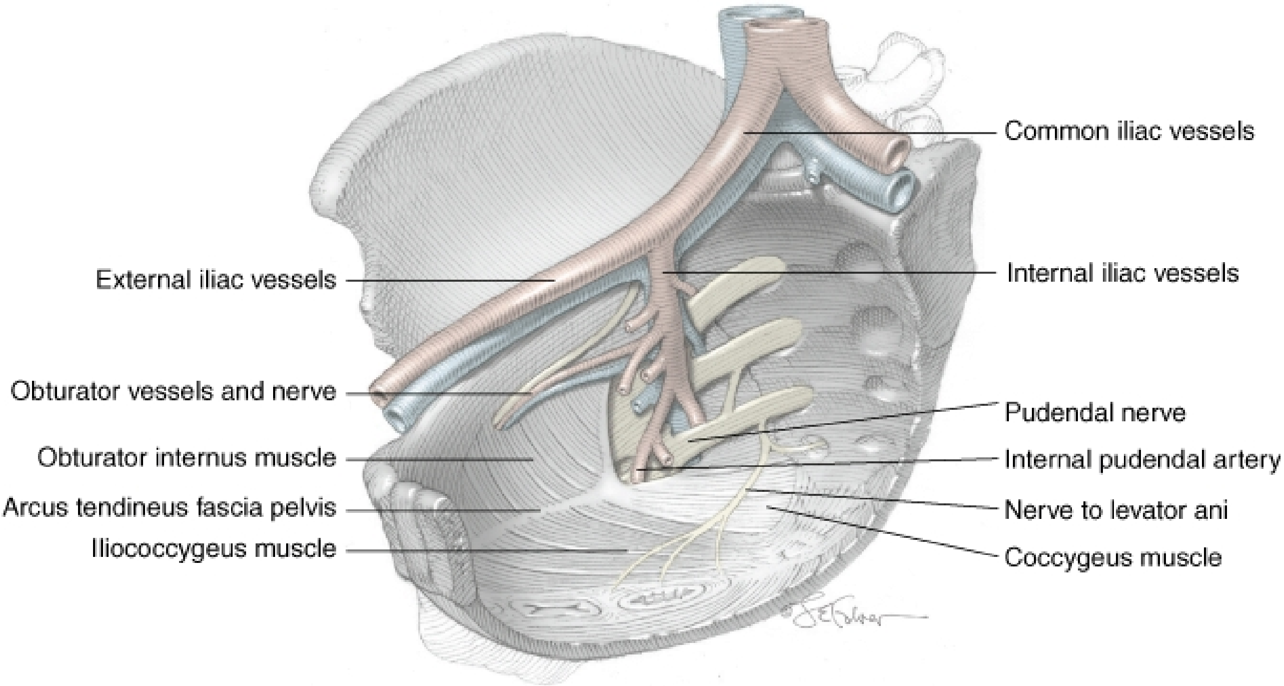
ANAL SPHINCTER COMPLEX

This neuromuscular complex consists of the internal and external anal sphincter muscles and the puborectalis muscle (see Fig. 38-21). Of these, the internal anal sphincter (IAS) is the thickened distal 3- to 4-cm longitudinal extension of the colon's circular smooth muscle layer. It is innervated by the autonomic nervous system and provides 70 to 85 percent of the anal canal's resting pressure (Frenckner, 1975). As a result, the IAS contributes substantially to the maintenance of fecal continence at rest.

The external anal sphincter (EAS) consists of striated muscle and is primarily innervated by somatic motor fibers that course in the inferior rectal branch of the pudendal nerve (see Fig. 38-28). The EAS provides the anal canal's *squeeze pressure* and is mainly responsible for maintaining fecal continence when continence is threatened. At times, squeeze pressure may be voluntary or may be induced by increased intra-abdominal pressure. In addition, although resting sphincter tone is generally attributed to the IAS, the EAS maintains a constant state of resting contraction and may be responsible for approximately 25 percent of anal resting pressure. During defecation, however, the EAS relaxes to allow stool passage.

The puborectalis muscle is part of the levator ani muscle complex and is innervated from its pelvic surface by direct efferents from the third, fourth, and fifth sacral nerve roots (Fig. 25-1) (Barber, 2002). Its constant tone contributes to the anorectal angle, which aids in preventing rectal contents from entering the anus (see Fig. 38-9). Similar to the EAS, this muscle can be contracted voluntarily or in response to sudden increases in abdominal pressure.

FIGURE 25-1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Innervation of the female pelvic floor muscles from direct branches of S3 through S5.

The role of the puborectalis in maintaining stool continence remains controversial. However, it is best appreciated in women who remain continent of solid stool despite absence of the anterior portion of the external and internal sphincters, as can be seen in those with chronic fourth-degree lacerations (Fig. 25-2). With normal functioning of this muscle, evacuation is generally associated with a greater (or less obtuse) anorectal angle as the puborectalis relaxes. Conversely, paradoxical contraction of the puborectalis muscle during defecation may lead to impaired evacuation. Moreover, atrophy of this muscle has been associated with fecal incontinence (Bharucha, 2004).

FIGURE 25-2

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Chronic fourth degree laceration with complete absence of the perineal body and anterior portion of external anal sphincter (cloacal deformity). Skin dimples at 3 and 9 o'clock (**arrows**) indicate site of retracted ends of external anal sphincter.

ANORECTAL SENSATION

Anorectal Innervation

Innervation to the rectum and anal canal is derived from the superior, middle, and inferior rectal autonomic nerve plexuses that contain sympathetic and parasympathetic components, and by intrinsic nerves present in the rectoanal wall. In addition, the inferior rectal branch of the pudendal nerve conveys sensory input from the lower anal canal and the skin around the anus (see Fig. 38-30). Sensory receptors within the anal canal and pelvic floor muscles can detect the presence of stool in the rectum as well as the degree of distention. Through these neural pathways, information regarding rectal distension and rectal contents can be transmitted and processed and the action of the sphincteric musculature coordinated.

Rectoanal Inhibitory Reflex

The *rectoanal inhibitory reflex* (RAIR) refers to the transient relaxation of the IAS and contraction of EAS induced by rectal distension when stool first arrives in the rectum. This reflex is mediated by the intrinsic nerves in the anorectal wall and allows the sensory rich upper anal canal to come in contact with or "sample"' the rectal contents (Whitehead, 1987). Specifically, *sampling* refers to the process whereby the internal anal sphincter (IAS) relaxes, often independently of rectal distension, allowing the anal epithelium to ascertain whether rectal contents are gas, liquid, or solid stools (Miller, 1988).

Following integration of this neural information, defecation can ensue in the appropriate social setting. Alternatively, if required,

defecation can generally be postponed, as the rectum can accommodate its contents, and the external anal sphincter (EAS) or puborectalis muscle or both can be voluntarily contracted. However, if rectal sensation is impaired, contents may enter the anal canal and may leak before the EAS can contract (Buser, 1986).

Evaluation of the RAIR may clarify the underlying etiology of AI. This reflex is absent in those with congenital aganglionosis (Hirschsprung's disease) but preserved in patients with cauda equina lesions or after spinal cord transection (Bharucha, 2006).

RECTAL ACCOMMODATION AND COMPLIANCE

Following anal sampling, the rectum can relax to admit the increased rectal volume in a process known as accommodation. The rectum is a highly compliant reservoir that aids storage of stool. As rectal volume increases, an urge to defecate is perceived. If this urge is voluntarily suppressed, the rectum relaxes to continue stool accommodation. A loss of compliance may decrease the ability of the rectal wall to stretch or accommodate, and as a result, rectal pressure may remain high. This may place increased demands on the other components of the continence mechanism such as the anal sphincter complex.

Rectal compliance can be calculated by measuring the sensitivity and maximal volume tolerated in a fluid-filled balloon during anorectal manometry (Anorectal Manometry). Rectal compliance may be decreased in those with ulcerative and radiation proctitis. In contrast, increased compliance may be noted in certain patients with constipation, potentially signaling a megarectum.

Incontinence Risks

Causes of AI and defecatory disorders are diverse and are likely multifactorial. These conditions develop if structural and/or functional components of continence and defecatory mechanisms are altered (Table 25-1).

Table 25-1 Risk Factors for Fecal Incontinence
Obstetric
Increasing parity
Anal sphincter damage
Other medical conditions
Increasing age
Increasing body mass index
Postmenopausal status
Diabetes
Chronic hypertension
Chronic obstructive pulmonary disease
Stroke
Scleroderma
Prior pelvic radiation therapy
Medications
Urogynecologic

Urinary incontinence
Pelvic organ prolapse
Gastrointestinal
Constipation
Diarrhea
Fecal urgency
Food intolerance
Irritable bowel syndrome
Prior anal abscess or fistula
Prior anal surgery
Neuropsychiatric
Spinal cord injury
Parkinson disease
Prior spinal surgery
Multiple sclerosis
Myopathies
Cognitive dysfunction
Psychosis

OBSTETRIC

In younger, reproductive-aged women, the most common association with AI is vaginal delivery and damage to the anal sphincter muscles (Snooks, 1985; Sultan, 1993; Zetterstrom, 1999). This damage may be mechanical or neuropathic and can result in early fecal and flatal incontinence.

Rates of sphincter tear during vaginal births in the United States range from 6 to 18 percent (Fenner, 2003; Handa, 2001). A recent multicenter trial conducted by the Pelvic Floor Disorders Network prospectively evaluated bowel continence status in primiparous women delivered at term in the United States. Their results showed that at both 6 weeks and 6 months postpartum, women who sustained anal sphincter tears during vaginal delivery had twice the risk of FI and reported more severe FI compared with women who delivered vaginally without evidence of sphincter disruption (Borello-France, 2006). In contrast, a retrospective study evaluated 151 women with diverse obstetric histories who delivered 30 years previously. Women with a prior sphincter disruption were more likely to have "bothersome"' flatal incontinence, but were not at increased risk for FI compared with women who had an isolated episiotomy or those who underwent cesarean delivery (Nygaard, 1997). Thus, other mechanisms associated with pregnancy and factors associated with aging may contribute to AI regardless of delivery mode.

OTHER FACTORS

Inflammatory bowel conditions and radiation therapy involving the rectum can result in poor compliance and loss of accommodation. Of these patients, those with inflammatory bowel disease and chronic diarrhea are more frequently affected. Liquid stool is more difficult to control than solid, and thus FI may develop in these women even if all components of the continence mechanism are grossly intact. Alternatively, chronic constipation with straining at stool may result in damage to the muscular and/or neural components of the sphincter mechanism. Similarly, other neuromuscular injury to the puborectalis and/or anal sphincter muscles, such as that associated with pelvic organ prolapse may lead to AI.

Nervous system dysfunction in those with spinal cord injury, back surgery, multiple sclerosis, diabetes, or cerebrovascular accident may lead to poor accommodation, loss of sensation, impaired reflexes, and myopathy. Finally, loss of rectal sensation can be seen with normal aging.

Diagnosis

Precise identification of the underlying cause and accurate assessment of symptom severity are essential prior to selecting an appropriate treatment plan. A complete history and physical examination should always be the first step in evaluating patients with AI, and often leads to identification of correctable problems. Following examination, anal endosonography is usually obtained to identify anal sphincter anatomic defects that may be amenable to surgery. Other selected tests, which are described below, may be added as clinically indicated. However, because current surgical outcomes are less than optimal, most patients, even those with anatomic defects, are initially treated conservatively.

HISTORY

A thorough history should include incontinence duration and frequency, stool consistency, timing of incontinent episodes, use of sanitary protection, and social impact of incontinence. Additionally, questioning should address risk factors noted in Table 25-1. Importantly, urge-related AI should be differentiated from incontinence without awareness, as these may be associated with different underlying pathologies. Additionally, urgency without incontinence may reflect inability of the rectal reservoir to store stool rather than a sphincteric disorder.

Validated Questionnaires

Several incontinence-scoring systems have been developed that provide objective measures of a patient's degree of incontinence. The fecal incontinence severity index (FISI) is a brief, validated instrument used to determine AI severity (Table 25-2) (Rockwood, 1999). In addition, the validated fecal incontinence quality of life (FIQL) questionnaire is designed to estimate the impact of fecal incontinence on lifestyle, coping behavior, depression/self-perception, and embarrassment (Table 25-3) (Rockwood, 2000). These validated questionnaires may be used diagnostically but also following treatment to determine response.

Table 25-2 Fecal Incontinence Severity Index

	Two or More Times Daily	Once Daily	Two or More Times Weekly	Once Weekly	1â€“3 Times Monthly	Never
Gas	☐	☐	☐	☐	☐	☐
Mucus	☐	☐	☐	☐	☐	☐
Liquid stool	☐	☐	☐	☐	☐	☐
Solid stool	☐	☐	☐	☐	☐	☐

From Rockwood, 1999, with permission.

Table 25-3 Fecal Incontinence Quality of Life Scale Composition

Scale 1: Lifestyle

- I cannot do many of the things I want to do
- I am afraid to go out
- It is important to plan my schedule (daily activities) around my bowel pattern
- I cut down on how much I eat before I go out
- It is difficult for me to get out and do things like going to a movie or to church
- I avoid traveling by plane or train
- I avoid traveling
- I avoid visiting friends
- I avoid going out to eat
- I avoid staying overnight away from home

Scale 2: Coping/Behavior

- I have sex less often than I would like to
- The possibility of bowel accidents is always on my mind
- I feel I have no control over my bowels
- Whenever I go someplace new, I specifically locate where the bathrooms are
- I worry about not being able to get to the toilet in time
- I worry about bowel accidents
- I try to prevent bowel accidents by staying very near a bathroom
- I can't hold my bowel movement long enough to get to the bathroom
- Whenever I am away from home, I try to stay near a restroom as much as possible

Scale 3: Depression/Self-perception

- In general, how would you say your health is
- I am afraid to have sex
- I feel different from other people
- I enjoy life less
- I feel like I am not a healthy person
- I feel depressed
- During the past month, have you felt so sad, discouraged, hopeless, or had so many problems that you wondered if anything was worthwhile

Scale 4: Embarrassment

- I leak stool without even knowing it
- I worry about others smelling stool on me
- I feel ashamed

Adapted from Rockwood, 2000, with permission.

PHYSICAL EXAMINATION

Examination should begin with careful inspection of the anus and perineum, looking for stool soiling, scars, perineal body length, hemorrhoids, anal warts, rectal prolapse, dovetail sign, or other anatomic abnormalities (Fig. 25-3). The perianal skin is gently stroked with a cotton-tipped swab, and the cutaneous anal reflex, also colloquially termed *anal wink,* should be noted. This finding provides gross assessment of pudendal nerve integrity.

FIGURE 25-3

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photograph showing the dovetail sign, which is created by disruption of the anterior portion of external anal sphincter (EAS). Radial skin spikes are typically formed by attachment of skin to the EAS, but are commonly absent from 10 to 2 o'clock* in those with this disruption.

With digital rectal examination, one can assess IAS resting tone, sample for gross or occult blood, and palpate masses or fecal impaction. In addition, squeeze pressure can subjectively be assessed during voluntary patient contraction of the EAS around a finger inserted into the rectum. Lastly, patients performing a Valsalva maneuver can allow inspection for excessive perineal body descent, vaginal wall prolapse, and rectal prolapse (Fig. 25-4).

FIGURE 25-4

A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Patient at rest **(A)** and with Valsalva **(B)** , showing full-thickness rectal prolapse protruding through the anal opening.

DIAGNOSTIC TESTING

Enema

A tap water enema is a simple test that may be used to determine if a patient is truly incontinent. Liquid stool is more difficult to control than solid stool, and thus patients who can hold enema contents for several minutes are not likely to have significant FI. In these instances, other etiologies for their symptoms should be sought.

Anorectal Manometry

During this test, a small flexible tube containing an inflatable balloon tip and pressure transducer is inserted into the rectum. Resting and squeeze pressures of the anal canal are then measured at incremental points as the balloon is slowly withdrawn from the rectum (Fig. 25-5). As an additional test, pressures may also be measured as a patient simulates defecation and expels the catheter balloon tip. In sum, anorectal manometry allows assessment of: (1) anal sphincter function, (2) reflexes, (3) rectal compliance, and (4) rectal sensation (Table 25-4).

Table 25-4 Functional Testing for Patients with Fecal Incontinence[a]

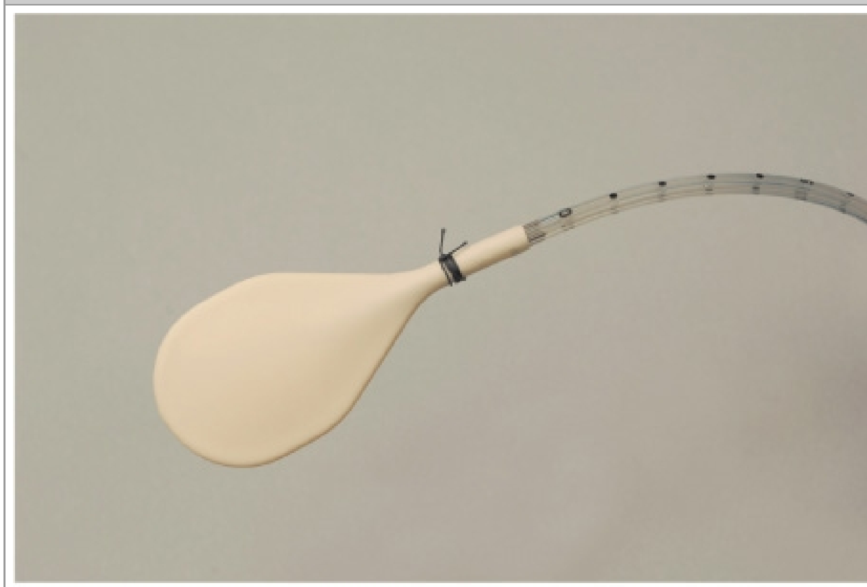
Factors of Relevance in FI	Manometry: Anal Resting Pressure	Manometry: Anal Squeeze Pressure	Manometry: Rectal Perception	Manometry: Rectal Compliance	Defecography	EAUS	E
Anal sphincters							
Internal	+					+	
External		+				+	+
Puborectalis					+		+
Rectum							
Perception			+				
Compliance				+			
Reservoir function			+	+	+		
Megarectum			+		+		
Pelvic floor							
Perineal descent					+		
Anorectal angle					+		
Neural							
Pudendal nerve		+					+

[a] A plus sign indicates an appropriate test for a particular component of continence.

EAUS = endoanal ultrasonography; EMG = electromyography; FI = fecal incontinence.

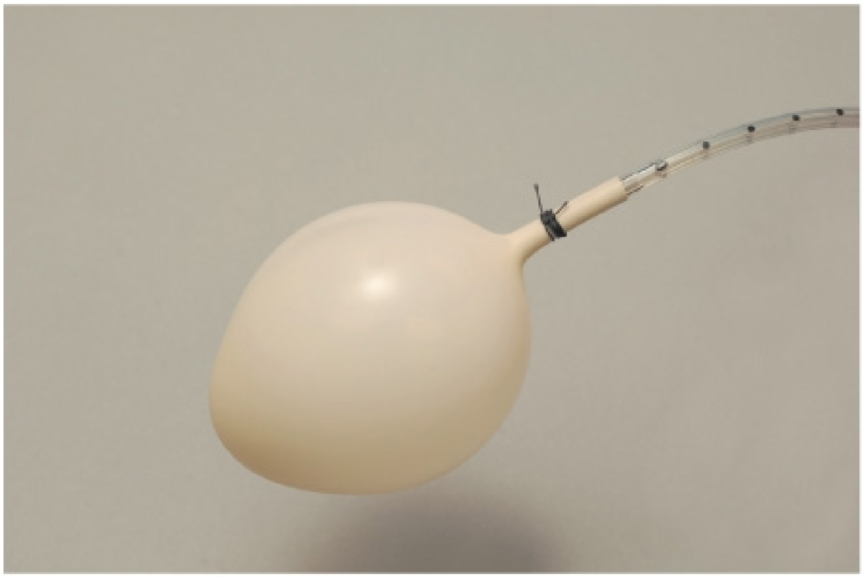
From Hinninghofen, 2003, with permission.

FIGURE 25-5



A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Manometry tube and balloon, empty **(A)** and after filling **(B)** .

During evaluation of the sphincters, manometry objectively measures IAS resting pressure and EAS squeeze pressure. Decreased pressure readings may indicate structural disruption, myopathy, or neuropathy.

Sphincter reflexes are also assessed during pressure measurements. During balloon insufflation, relaxation of the IAS should accompany rectal distention via the rectoanal inhibitory reflex (RAIR).

Rectal compliance and sensation may be determined by sequentially inflating a rectal balloon to various volumes. Decreased rectal compliance may be noted by an inability to inflate a balloon to typical volumes without patient discomfort. This may indicate a rectal reservoir that is unable to appropriately store stool. In contrast, decreased perception of balloon insufflation may indicate neuropathy.

One of the main limitations with manometry is that normal values may be seen in incontinent patients and vice versa. Despite this disadvantage, anal manometry serves an important role in the evaluation of AI.

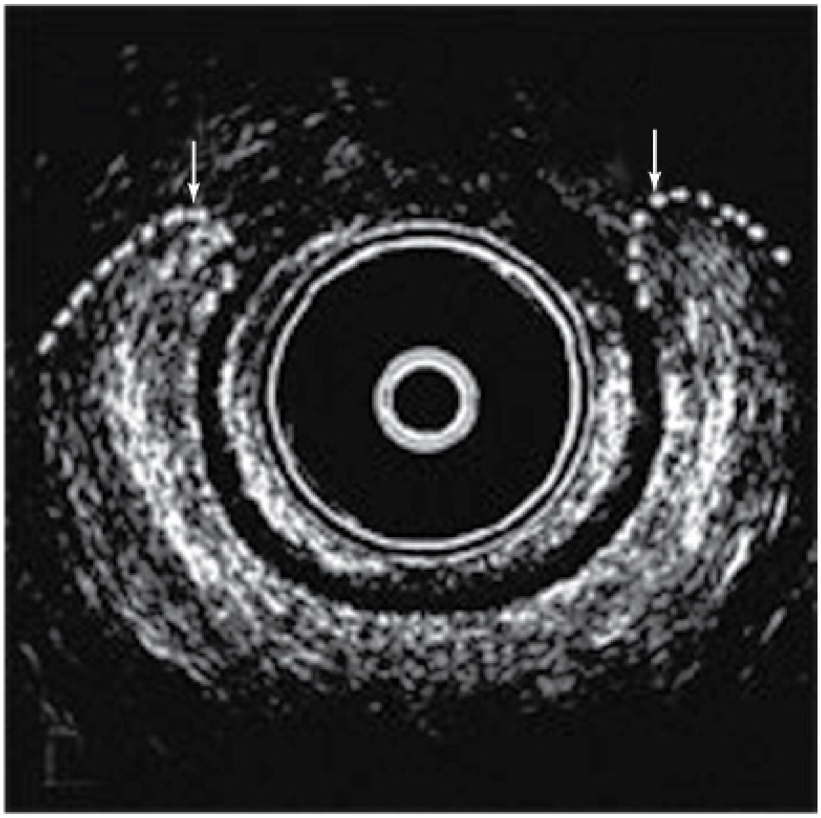
Endoanal Ultrasonongraphy

Also known as, *transanal sonography,* this technique was introduced in 1989 and is now the primary diagnostic imaging technique to evaluate the integrity, thickness, and length of the internal and external anal sphincters (Fig. 25-6). This tool allows diagnosis of sphincter defects in women with occult defects from obstetric trauma who in the past were labeled as having "idiopathic"' FI and who may not have been considered for surgical correction. The technique uses a rotating endoprobe with a 10-MHz transducer, which provides a 360-degree evaluation of the anal canal.

FIGURE 25-6

A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Endoanal ultrasonography in a woman with normal anal sphincters **(A)** and anterior defects of the external and internal anal sphincter muscles **(B)** . **Dashed lines** and **arrows** in B illustrate the ends of the torn EAS. IAS = internal anal sphincter; EAS = external anal sphincter.

In addition, this modality can image the puborectalis muscle and perineal body. A recent study by Oberwalder and colleagues (2004) showed that in a group of incontinent women, perineal body thickness of less than or equal to 10 mm was associated with anal sphincter defects in 97 percent of cases. In contrast, perineal body thickness of 10 mm to 12 mm was associated with sphincter defects in one third of patients with FI. Perineal body thickness greater than 12 mm was infrequently associated with these defects.

Magnetic Resonance (MR) Imaging

Endoanal magnetic resonance (MR) imaging is typically done with an anal endocoil. This modality is more expensive than anal endosonography, and its value for anal sphincter evaluation is controversial. Although sonography has been shown to be more sensitive in detecting IAS abnormalities, MR imaging is more sensitive in visualizing EAS morphology including atrophy (Beets-Tan, 2001; Rociu, 1999). This may have value preoperatively, as patients with EAS atrophy may have poorer results following anal sphincteroplasty compared with those without atrophy (Briel, 1999). However, the role of endocoil MR imaging in the assessment of AI is yet to be determined. Recent evidence from a National Institutes of Health (NIH)-funded trial within the Pelvic Floor Disorders Network (PFDN) has challenged the reproducibility of MR imaging in detecting anal sphincter defects.

A second MR imaging modality, termed *dynamic MR imaging* allows dynamic examination of rectal emptying and evaluation of pelvic floor muscles, including the puborectalis muscle, during rest, squeeze, and defecation. It simultaneously permits pelvic organ prolapse assessment. This current research tool, however, is technically difficult and other than avoiding the ionizing radiation

associated with evacuation proctography, this technique offers no advantage for studying rectal function in the clinical setting.

Evacuation Proctography

During this radiographic test, also known as *defecography,* the rectum is opacified with a thick barium paste, and the small bowel fills with a barium suspension given orally. Radiographs or fluoroscopic imaging is then obtained while a patient is resting, contracting their sphincter, coughing, and straining to expel the barium.

This test of dynamic rectal emptying and anorectal anatomy is not widely used to assess evacuation disorders unless obstructive causes for AI are suspected. Accordingly, it may be obtained if intussusception, internal rectal prolapse, or enteroceles are concerns.

Electromyography

This test graphically records electrical activity of muscles at rest and during contraction. During electromyography (EMG), needle electrodes are inserted through the skin into a muscle, and electrical activity detected by these electrodes is displayed graphically. In evaluation of AI, EMG may be used to assess the neuromuscular integrity of the EAS and puborectalis muscle. Specifically, by measuring action potentials from muscle motor units, EMG can help clarify which portions of these muscles are contracting and relaxing appropriately. Additionally, following injury, muscle may be partially or completely denervated, and compensatory re-innervation may then follow. Patterns characteristic of such denervation and re-innervation may be identified with EMG.

Surface Electromyography

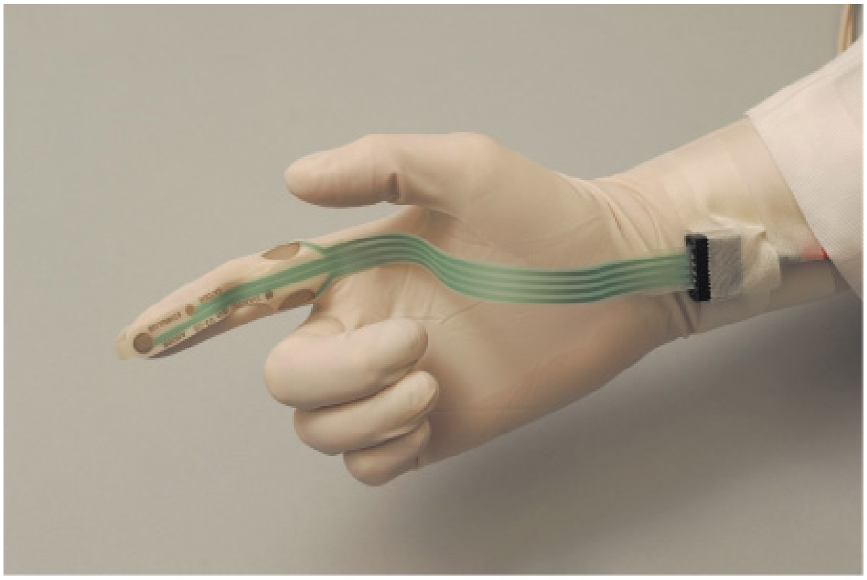
For EMG testing, concentric-needle, single-fiber, or surface EMG can be used. Needle EMG is primarily used in research, whereas surface EMG is most commonly used in clinical settings. Unlike needle electrodes, surface electrodes are placed next to the anus, cause little discomfort to the patient, and carry no risk of infection. This technique provides useful information regarding sphincter innervation and can be used during biofeedback to give visual or auditory signals to patients.

Pudendal Nerve Terminal Motor Latency Test

This stimulation test of the pudendal nerve measures the time delay between electrical nerve stimulation and EAS motor response. This delay, also termed *latency,* if prolonged, may indicate pudendal nerve pathology, which may be a cause of AI.

During pudendal nerve motor latency (PNML) testing, an electrode positioned on an examiner's fingertip is connected to a pulsed-stimulus generator (Fig. 25-7). The pudendal nerves are transanally stimulated through the lateral walls of the rectum at the level of the ischial spines. The action potential response of the EAS is received by an electrode at the base of the examining finger and registered on an oscilloscope.

FIGURE 25-7



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Pudendal nerve motor latency (PTML) electrode connected to an examiner's finger.

Although PNML prolongation has been considered a marker of idiopathic fecal incontinence, this test provides little information regarding the etiology of fecal incontinence. Accordingly, it has been replaced by more specific and sensitive tests for sphincter muscle innervation such as EMG (Barnett, 1999). However, in patients with a sphincter defect who are candidates for repair, general sphincter neurologic status can be assessed by this test, and the results used in preoperative counseling. For example, patients with pudendal neuropathy may have poorer outcomes after anatomic sphincter re-approximation compared with those without nerve dysfunction (Gilliland, 1998).

Colonoscopy and Barium Enema

Based on the history and physical examination, these tests may be indicated to exclude inflammatory bowel conditions or malignancy.

Treatment

The goal of treatment is to restore or improve fecal continence and improve patient quality of life. Treatment is highly individualized and dependent on the etiology and severity of AI, available treatment options, and patient health.

NONSURGICAL

Most patients with AI, excluding those with an obvious anal sphincter defect and significant FI, may benefit from conservative management. This may include diet modification, constipating agents, bulking agents, timed enemas or suppositories, and biofeedback.

Medical Management

A recent Cochrane review of randomized or quasi-randomized controlled trials analyzed the use of pharmacologic agents for the treatment of FI in adults. Of these trials, most focused on diarrheal treatment, rather than FI, and thus, limited data are available to guide clinicians in drug therapy selection (Cheetham, 2003). However, for patients with minor incontinence, the use of bulking agents can change stool consistency and create feces that are firmer and easier to control (Table 25-5). Common side effects such as abdominal distension and bloating can be improved by starting with smaller doses or switching to a different agent.

Table 25-5 Medical Management of Fecal Incontinence

Treatment	Brand Name	Oral Dosage	Manufacturer
Bulking agents			
Psyllium	Metamucil	1 tbsp. mixed into 8 oz. of water 1â€“3 times daily	Proctor and Gamble
Psyllium	Konsyl	1 tsp. mixed into 8 oz. of water 1â€“3 times daily	Konsyl Pharmaceuticals
Methycellulose	Citrucel	1 tbsp. mixed into 8 oz. of water 1â€“3 times daily	GlaxoSmithKline
Loperamide hydrochloride	Imodium	2â€“4 mg, 1â€“4 times daily to a maximum daily dose of 16 mg	McNeil PPC
Diphenoxylate hydrochloride	Lomotil	5 mg, 1â€“4 times daily to a maximum daily dose of 20 mg	Pfizer
Amitriptyline	Generic	10â€“25 mg at bedtime; increase by 10â€“25 mg weekly up to 75â€“150 mg at bedtime or a therapeutic drug level	

Agents that slow fecal intestinal transit time such as loperamide hydrochloride can reduce stool volume in patients with diarrhea and FI by increasing the time available for removal of fluid from stool. This agent has also been shown to increase anal resting tone, and therefore, may even be beneficial for patients with FI and no diarrhea (Read, 1982). Side effects are uncommon.

Diphenoxylate hydrochloride is used in the same capacity as loperamide hydrochloride and dosing is similar. Although this is a schedule V substance, the potential for physical dependence is minimal.

Finally, amitriptyline is a tricyclic antidepressant that has been used to treat idiopathic FI. Although the mechanism of action is poorly understood, some of its beneficial effects may be related to its anticholinergic properties.

Bowel Management

Daily, timed, tap water enemas or glycerin or bisacodyl suppositories (Dulcolax, Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT) may be used to empty the rectum after eating. These provide acceptable and helpful options for some patients. Bulking agents can be used concurrently with these evacuation methods to diminish stooling between desired defecations.

Biofeedback and Pelvic Floor Therapy

Many behavioral techniques, often considered together as biofeedback, measure physiologic signals such as muscle tension and then display them to a patient in real time. In general, visual, auditory, and/or verbal feedback cues are directed to the patient during these therapy sessions. Thus, candidates typically include those whose cognitive function is intact, who can follow commands, and who are motivated.

Biofeedback is usually selected to increase neuromuscular conditioning. Specifically, for FI, goals of therapy are to improve anal sphincter strength, sensory awareness of stool presence, and coordination between the rectum and the anal sphincter (Rao, 1998). Treatment protocols are individualized and dictated by the underlying dysfunction. Accordingly, the number and frequency of sessions required for improvement varies but commonly three to six 1-hour, weekly or bi-weekly appointments are needed. In many cases, reinforcing sessions at various subsequent intervals are also recommended.

Biofeedback has been noted to be an effective treatment for FI, and symptomatic improvement has been reported in up to 80 percent of treated patients (Engel, 1974; Jensen, 1997; Norton, 2001). However, in a review of biofeedback and pelvic floor exercises for FI, Norton and colleagues (2001) found insufficient evidence to draw conclusions regarding the benefit of biofeedback

for FI. Despite this, a large number of studies have shown positive outcomes for biofeedback in treating FI. Biofeedback is a benign and relatively inexpensive treatment compared with other medical interventions. Accordingly, it is often used to treat these disorders.

Pelvic Floor Muscle Strengthening Exercises

Also known as *Kegel exercises,* this technique alone has not been definitively shown to benefit patients with FI (Whitehead, 1985). However, they are safe and free of cost and may benefit some patients, especially if performed in conjunction with other therapies. These exercises are described further in Chapter 23, Pelvic Floor Strengthening Exercises.

SURGICAL

Given the potential for postoperative morbidity and the less less-than than-optimal results presently reported with available surgical procedures, surgery should be reserved for those patients with major structural abnormalities of the anal sphincter(s), severe symptoms, and those who fail to respond to conservative management.

Anal Sphincteroplasty

Repair of the EAS and/or IAS is most commonly performed in patients with acquired AI and an anterior sphincter defect following an obstetric or iatrogenic injury. Two methods may be used for sphincter repair and include an end-to-end technique and an overlapping method (see Section 42-25, Anal Sphincteroplasty). The end-to-end technique is most commonly used by obstetricians to re-approximate torn ends of an anal sphincter at delivery. However, in patients remote from delivery with a sphincter defect and FI, the overlapping technique is preferred by most colorectal surgeons and urogynecologists.

With the overlapping method performed remote from delivery, short-term continence improvements of up to 85 percent were previously reported (Fleshman, 1991; Sitzler, 1996). However, recent reports show significant deterioration of continence during long-term postoperative surveillance (Baxter, 2003; Bravo, 2004; Halverson, 2002; Malouf, 2000). The reason for this deterioration following initial improvement remains unknown. Hypotheses include aging, scarring, and progressive pudendal neuropathy related either to the initial injury or to the repair. Patients who fail to improve after anal sphincteroplasty and who are found to have a persistent sphincter defect may be candidates for a second sphincteroplasty. However, those with an intact sphincter following repair and persistent symptoms are only considered candidates for conservative management or one of the salvage or minimally invasive surgical procedures described later.

Currently, there is no conclusive evidence that the overlapping method, if used at delivery, leads to superior results than the traditional end-to-end method of anal sphincter repair (Fitzpatrick, 2000; Garcia, 2005). Moreover, overlapping repair requires increased technical skills and carries the potential for increased blood loss, operating time, and pudendal neuropathy. For these reasons, the end-to-end technique is likely to remain the standard method for sphincter re-approximation at delivery until further data from randomized controlled trials are available. Importantly, given the strong association between anal sphincter lacerations and development of AI, emphasis should continue to focus on primary prevention of these lacerations.

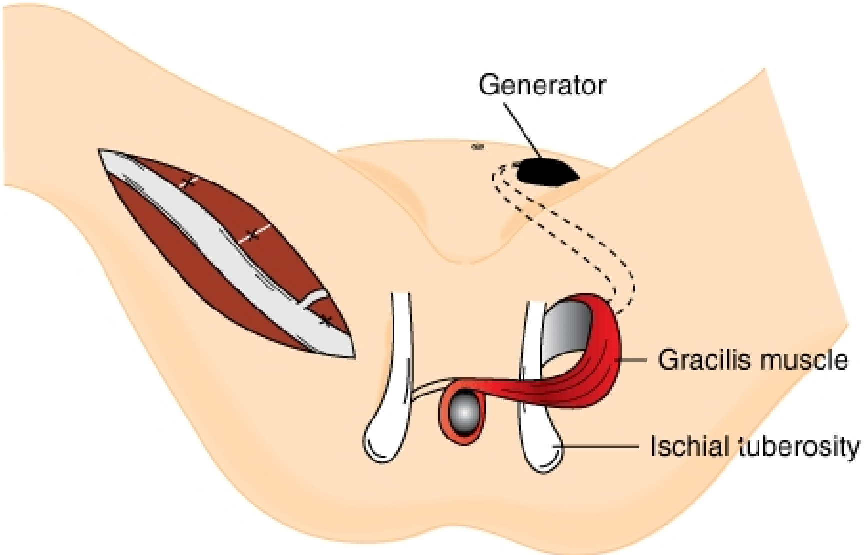
Postanal Pelvic Floor Repair

This repair is advocated for patients who have significant FI with no evidence of sphincter defects or neuropathy and who fail to improve with conservative management. The procedure is designed to re-establish the anorectal angle and to lengthen and tighten the anal canal. Through an intersphincteric approach, sutures are placed between the ends of the iliococcygeus, pubococcygeus, puborectalis, and external anal sphincter muscles. Although Parks originally reported incontinence improvement in up to 80 percent of patients, similar results have not been replicated (Parks, 1975; Browning, 1983).

Gracilis Muscle Transposition

This procedure is advocated for patients who have failed sphincter repair or those with a sphincter defect too large to allow muscle re-approximation (Baeten, 1991). *Dynamic graciloplasty* involves separating the gracilis tendon from its point of insertion at the knee, wrapping the muscle around the anus, and attaching the tendon to the contralateral ischial tuberosity (Fig. 25-8). The muscle is then stimulated with an electrical pulse generator that is implanted in the abdomen.

FIGURE 25-8



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

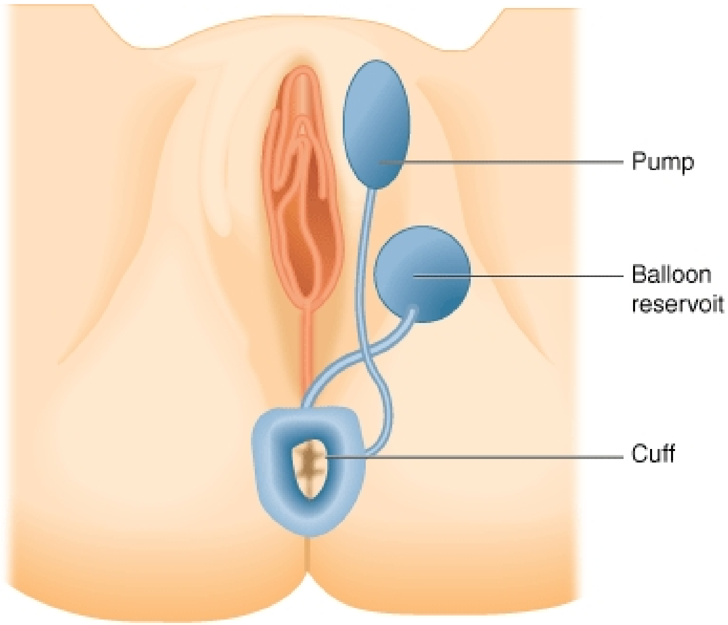
Dynamic graciloplasty. Note the gracilis muscles wrapped around the anus and attached to contralateral ischial tuberosity.

This procedure has a significant performance learning curve and is offered in only a few medical centers that have adequate patient volume and surgical experience. Complication rates of greater than 50 percent have been reported and overall success rates range below 35 percent (Chapman, 2002; Matzel, 2001; Thornton, 2004; Wexner, 2002). However, it is an acceptable option for many patients whose only alternative is a permanent stoma. This procedure is not currently performed in the United States, as the generator used to stimulate the gracilis muscle is not available.

Artificial Anal Sphincters

This procedure was first reported by Christiansen and Lorentzen in 1987 and is still considered experimental by many. It is indicated for patients with severe incontinence who have failed other treatment methods (Fig. 25-9). An inflatable cuff that mimics the function of the anal sphincter is implanted around the anus; a pressure-regulating balloon is implanted within the abdominal wall or iliac fossa; and a control pump is placed in the scrotum or the labia. When fully inflated, the cuff occludes the anal canal. This procedure carries a high rate of complications and subsequent implant removal. Similarly to the muscle transposition procedures, it has a considerable learning curve for most surgeons (Devesa, 2002; Parker, 2003).

FIGURE 25-9



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Artificial anal sphincter.

Diversion (Colostomy or Ileostomy)

Diversion is reserved for patients with incapacitating FI who have failed other treatments (see Sections 43-15, Colostomy and 43-17, Ileostomy). For these selected patients, such procedures can significantly improve their quality of life.

MINIMALLY INVASIVE PROCEDURES FOR FECAL INCONTINENCE

Secca Procedure

This outpatient procedure is currently used in the United States to treat FI in patients with no evidence of sphincter defects or pudendal neuropathy. It involves delivery of temperature-controlled radiofrequency energy to the anal sphincter muscles by means of a specifically designed anoscope. Resulting tissue heating is believed to cause heat-induced collagen contraction followed by focal wound healing, remodeling, and tightening. In a multicenter study, Efron and colleagues (2003) showed a median 70 percent resolution of symptoms in 50 patients.

Sacral Nerve Stimulation

Sacral neuromodulation is presently used in the United States to treat selected cases of urge incontinence, urgency-frequency syndrome, and idiopathic nonobstructive urinary retention (see Section 42-12, Sacral Neuromodulation). This procedure is also currently under investigation for the treatment of FI (Ganio, 2001; Matzel, 1995, 2004). Although the mechanism of action remains unclear, some preliminary studies have shown a nearly 80-percent success rate for FI. As a result, there is tremendous enthusiasm and anticipation of further study results.

FUNCTIONAL ANORECTAL DISORDERS

In the current classification of functional gastrointestinal disorders, three functional anorectal disorders are recognized: (1) functional fecal incontinence (FI), (2) functional anorectal pain, and (3) functional defecation disorders (Table 25-6) (Drossman, 2006). Criteria for these and other functional GI disorders have been defined by the Rome III Foundation expert consensus organization. As shown in Table 25-6, these are primarily diagnosed based on patients' reported symptoms. As with other functional disorders, organic disease should be excluded prior to assignment of these diagnoses.

Table 25-6 Rome III Criteria of Functional Gastrointestinal Disorders
FUNCTIONAL ANORECTAL DISORDERS
Functional fecal incontinence
Functional anorectal pain
Chronic proctalgia
Levator ani syndrome
Unspecified functional anorectal pain
Proctalgia fugax
Functional defecation disorders
Dyssynergic defecation
Inadequate defecatory propulsion

Adapted from Drossman, 2006, with permission.

Functional Fecal Incontinence

Functional FI is defined by Rome III criteria as recurrent uncontrolled passage of fecal material for more than 3 months in an individual with anatomically normal defecatory muscles that function abnormally. As a result, fecal retention or diarrhea is common, and psychological disorders may be associated. The etiology is varied and causes may include disturbed intestinal motility, poor rectal compliance, impaired rectal sensation, and weakened pelvic floor muscles (Whitehead, 2001). Once diagnosed, functional FI is primarily treated with medical management or biofeedback, as described earlier.

Functional Anorectal Pain

Categories within this group are differentiated from one another by the duration of pain and by the presence or lack of associated puborectalis muscle tenderness. *Levator ani syndrome,* also known as *levator ani spasm,* usually presents as a pressure sensation or ache in the upper rectum. Rome III criteria require that symptoms are present for more than 3 months; episodes should last at least 20 minutes; and symptoms are associated with puborectalis muscle tenderness when palpated. In contrast, *proctalgia fugax* presents as sudden, severe anal or lower rectal pain that lasts for a few seconds to a few minutes. Pain may disrupt normal activities but episodes occur rarely more than 5 five times a year.

Treatments for levator ani syndrome are varied and may include, among others, trigger point release maneuvers, biofeedback, local heat, and pharmacologic agents such as nonsteroidal anti-inflammatory drugs, other analgesics, muscle relaxants, and tranquilizers (see Chap. 11, Treatment). In contrast, proctalgia fugax is typically managed with reassurance.

Functional Defecation Disorders

This group of disorders includes: (1) dyssynergic defecation and (2) inadequate defecatory propulsion disorders. *Dyssynergic defecation* is also called pelvic floor dyssynergia, anismus, outlet obstruction constipation, or spastic pelvic floor syndrome. It is

characterized by failed relaxation of the puborectalis muscle and EAS, which is needed for normal defecation. This condition is common and is thought to account for 25 to 50 percent of chronic constipation cases (Wald, 1990). Symptoms include chronic straining and impaired or incomplete evacuation. Diagnosis requires confirmation by EMG, manometry, or radiologic testing of persistent contraction of these muscles during attempted defecation. Other causes of constipation should also be excluded. Biofeedback interventions for dyssynergic defecation teach patients to relax their pelvic floor muscles while simultaneously applying downward intra-abdominal pressure (Valsalva maneuver).

RECTOVAGINAL FISTULA

Definition and Classification

Rectovaginal fistulas (RVFs) are congenital or acquired epithelial-lined tracts between the vagina and rectum. They are classified according to their location, size, and etiology. All of these features aid in selecting the appropriate management and in predicting outcome of surgical repair. The underlying cause of a fistula is believed to be the most important predictor of a successful outcome, as it takes into account tissue and overall patient health.

Most RVFs are related to obstetric events and occur in the distal third of the vagina just above the hymen (Fig. 25-10 and Table 25-7) (Greenwald, 1978; Lowry, 1988; Tsang, 1998). Defects can range from less than 1 mm to several centimeters in diameter, and most communicate with the rectum at or above the dentate line. In contrast, fistulas with an opening below the dentate line are also appropriately called *anovaginal fistulas.* Surgical management of these "low" RVFs depends on the condition of the EAS, but it is usually achieved by a perineal (transvaginal or transanal) approach. Midlevel RVFs are found in the middle third of the vagina, whereas high rectovaginal fistulas have their vaginal communication close to the cervix or the vaginal cuff. In cases with high RVFs, fistulas may open into the sigmoid colon. These fistulas may not be readily seen on examination and often require contrast or endoscopic studies for diagnosis and an abdominal approach for repair.

FIGURE 25-10

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Rectovaginal fistula in distal wall of posterior vagina in a woman who sustained a fourth-degree perineal laceration.

Table 25-7 Rectovaginal Fistula Risk Factors
Obstetric complications
Third- or fourth-degree laceration repair dehiscence
Unrecognized vaginal laceration during operative vaginal or precipitous delivery
Inflammatory bowel disease
Most commonly Crohn disease
Ulcerative colitis less common, as it is not a transmural disease
Infection
Most commonly cryptoglandular abscess located in the anterior aspect of the anal canal
Lymphogranuloma venereum
Tuberculosis
Bartholin abscess
Human immunodeficiency virus infection
Diverticular disease
Previous surgery in the anorectal area
Hemorrhoidectomy
Low anterior resection
Excision of rectal tumors
Hysterectomy
Posterior vaginal wall repairs
Pelvic radiation therapy
Neoplasm
Invasive cervical or vaginal cancer
Anal or rectal cancer
Trauma
Intraoperative
Coital

Diagnosis

PATIENT HISTORY

Patients with RVF usually complain of flatus or stool leakage per vagina. They may also present with recurrent bladder or vaginal infection, rectal or vaginal bleeding, and pain. Presenting symptoms are often suggestive of the underlying etiology. For example, patients with obstetric injury and large defects of the anterior portion of the anal sphincters may present with gross fecal incontinence. In contrast, those with an infectious or inflammatory process may complain of diarrhea, abdominal cramping, and fevers.

PHYSICAL EXAMINATION

Most low RVFs can be visualized during inspection of the perineum and distal portion of the posterior vaginal wall. Rectovaginal examination allows assessment of the thickness of the perineal body and anovaginal wall and may allow palpation and visualization of the actual defect. Some RVFs that are not readily seen on initial examination can be identified by noting air bubbles at the fistula's vaginal opening after filling the vagina with water. Alternatively, methylene blue can be instilled in the rectum after a tampon is placed in the vagina. The fistula and a gross assessment of its location can be identified by inspecting the level of blue staining on the tampon following its removal.

DIAGNOSTIC TESTING

If the fistula site is not determined by the above maneuvers, a contrast study is indicated. These include barium enema and computed-tomography (CT) scanning. Alternatively, vaginoscopy may be performed. The vaginal is filled with sterile water or saline, the labia are closed, and a small endoscope is inserted vaginally to inspect the walls.

Unless RVFs are obviously due to a prior obstetric event, a biopsy of the fistulous tract is indicated to investigate possible malignancy and inflammatory conditions. In addition, proctoscopy or colonoscopy is warranted if inflammatory bowel disease, malignancy, or infection is suspected or cannot be excluded.

Treatment

Treatment of RVF depends on the underlying etiology and the defect's size and location. Some women with small RVFs following obstetric trauma may be followed conservatively in anticipation of spontaneous healing of the fistulous tract (Goldaber, 1993; Rahman, 2003). Larger obstetric-related defects and other low fistulas are most often corrected surgically. Surgical techniques include: (1) a transvaginal or transanal approach through episioproctotomy (conversion of the defect into a complete perineal tear or fourth-degree laceration); (2) a fistulotomy with a tension-free layered closure without episioproctotomy; or (3) a fistulotomy with transvaginal purse-string method of repair without episioproctotomy as described in (Section 42-26, Rectovaginal Fistula Repair (Fig. 25-11). Additionally, endorectal flap advancement is used by colorectal surgeons, primarily for the treatment of complex perianal fistulas such as those with tracts of greater than 2.5 cm in size or those related to trauma or infection (MacRae, 1995). With flap advancement, the fistulous tract is excised, a broad-based flap of rectal wall is employed to obliterate the fistula's origin, and division of the sphincter muscles is avoided. Of these methods, better outcomes have been shown following RVF repair using anal sphincteroplasties compared with endorectal advancement flap (Tsang, 1998).

FIGURE 25-11

A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Large rectovaginal fistula in a woman who underwent midline episiotomy. Note the fistula is above an intact external anal sphincter muscle.

Surgical repair of a fistula should be delayed until surrounding tissues are free of edema, induration, and infection (Wiskind, 1992). In addition, preoperative endoanal ultrasonography of the EAS is important in these patients. For example, an episioproctotomy should be avoided if the sphincter is intact (Hull, 2007).

Midlevel vaginal fistulas are also often due to obstetric trauma and are repaired transvaginally or transanally by a tension-free layered closure or an endorectal advancement flap. High fistulas are most commonly repaired by a transabdominal approach using bowel resection of the involved segment followed by primary bowel re-anastomosis.

Success rates vary depending on the underlying cause and method of repair. Successful repairs following obstetrical injury vary from 78 percent to 100 percent (Khanduja, 1999; Tsang, 1998). Success rates of 40 to 50 percent have been recently been reported with rectal advancement flaps, and of 74 percent with episioproctotomy (Mizrahi, 2002; Sonoda, 2002). Fistulas due to other etiologies such as radiation, cancer, or active inflammatory bowel disease are more difficult to treat successfully. In general, success rates are highest with the first surgical attempt at repair (Lowry, 1988).

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GENITOURINARY FISTULA

A genitourinary fistula is defined as an abnormal communication between the urinary (ureters, bladder, and urethra) and the genital (uterus, cervix, and vagina) systems. The true incidence of genitourinary fistula is unknown, although the generally accepted incidence approximates 1 percent or less of all genitourinary operations (Harris, 1995). This is most likely an underestimation because many are unreported or unrecognized. The most common type of genitourinary fistula is the vesicovaginal fistula and is discussed below (Goodwin, 1980).

Pathophysiology

Knowledge of the principles and phases of wound healing are important in understanding the pathogenesis of genitourinary fistula. After injury, tissue damage and necrosis stimulate inflammation, and the process of cell regeneration begins (Kumar, 2005). Initially at the injury site, new blood vessels form, termed *angiogenesis* . Three to five days after injury, fibroblasts proliferate and subsequently synthesize and deposit extracellular matrix, in particular collagen. This *fibrosis phase* determines the final strength of the healed wound. Collagen deposition peaks about seven days after injury and continues for a number of weeks. Subsequent maturation and organization of the scar, termed *remodeling* , augments wound strength. These phases are interdependent and are intrinsically involved in wound healing. Any disruption of this sequence eventually results in fistula formation. Most fistulas tend to present 1 to 3 weeks after tissue injury, a time during which tissues are most vulnerable to alterations in the healing environment, such as hypoxia, ischemia, malnutrition, radiation, and chemotherapy. Edges of the wound eventually epithelialize and a chronic fistulous tract is thus formed.

Classification

Although many classification systems exist for genitourinary fistula, there is no single accepted standardized scheme. Fistulas can develop at any point between the genital and urinary systems. Thus, one method of classification is based on anatomic communication (Table 26-1).

Table 26-1 Classification of Genitourinary Fistula Based on Anatomic Communication

	Urinary Tract		
	Ureter	**Bladder**	**Urethra**
Vagina	Ureterovaginal	Vesicovaginal	Urethrovaginal
	Vesicoureterovaginal		
Cervix	Ureterocervical	Vesicocervical	Urethrocervical
Uterus	Ureterouterine	Vesicouterine	Not reported

Vesicovaginal fistulas can also be characterized by their size and location in the vagina. They are termed *high vaginal* when found proximally in the vagina, *low vaginal* when noted distally, or *midvaginal* when identified centrally. For instance, post-hysterectomy vesicovaginal fistulas are often proximal or high in the vagina, and located at the level of the vaginal cuff.

Alternatively, some have classified vesicovaginal fistulas based on the complexity and extent of involvement (Elkins, 1999). In this scheme, complicated vesicovaginal fistulas are those that involve pelvic malignancy, prior radiation therapy, shortened vaginal length, or bladder trigone, or are distant from the vaginal cuff or greater than 3 cm in diameter.

In obstetric classification, high-risk vesicovaginal fistulas are described by their size (greater than 4 to 5 cm in diameter); involvement of urethra, ureter(*s*), or rectum; juxtacervical location with an inability to visualize the superior edge; and reformation following a failed repair (Elkins, 1999).

In addition, a surgical classification has been introduced as a method to objectively evaluate the repair of obstetric urinary fistulas (Waaldijk, 1995). In this system, type I fistulas are those that do not involve the urethral closure mechanism, type II fistulas do, and type III involve the ureter and include other exceptional fistulas. Type II fistulas are divided into: (A) without, or (B) with total or subtotal urethral involvement. Type IIB fistulas are further subdivided as to whether it is (a) without, or (b) with a circumferential defect.

Recently, a more comprehensive classification system has been proposed that integrates the fistula location in reference to a fixed point of anatomy, the size of the fistula, and the integrity of the surrounding tissues (Goh, 2004). In this scheme, genitourinary fistulas are initially divided into four types based on their distance from the external urethral meatus. They are further subdivided by the size of the fistula, the extent of scarring that surrounds the defect, and whether the vagina is reduced in length from scarring or from involvement of the fistula (Table 26-2).

Table 26-2 Classification of Genitourinary Fistula
This new classification divides genitourinary fistulae into four main types, depending on the distance of the fistula's distal edge from the external urinary meatus. These four types are further subclassified by the size of the fistula, extent of associated scarring, vaginal length, or special considerations.
Type 1: Distal edge of fistula >3.5 cm from external urinary meatus Type 2: Distal edge of fistula >2.5â€"3.5 cm from external urinary meatus Type 3: Distal edge of fistula 1.5â€">2.5 cm from external urinary meatus Type 4: Distal edge of fistula <1.5 cm from external urinary meatus
(a) Size <1.5 cm, in the largest diameter (b) Size 1.5â€"3 cm, in the largest diameter (c) Size >3 cm, in the largest diameter
i. None or only mild fibrosis (around fistula and/or vagina) and/or vaginal length >6 cm, normal capacity ii. Moderate or severe fibrosis (around fistula and/or vagina) and/or reduced vaginal length and/or capacity iii. Special consideration, e.g., postradiation, ureteric involvement, circumferential fistula, or previous repair.

From Goh, 2004, with permission.

Etiology

CONGENITAL

Congenital genitourinary fistulas are rare, with only ten cases reported in the literature (Asanuma, 2000). It is thought to result from either an abnormal fusion of the ureteric bud and the caudal end of the mÃ¼llerian duct with the urogenital sinus, or from incorporation of an aborted ureteric bud into a future wolffian duct remnant (see Chap. 18 and Fig. 18-1). These fistulas are

usually associated with other renal or urogenital abnormalities (Dolan, 2004).

ACQUIRED

Most vesicovaginal fistulas do not arise from developmental abnormalities but follow either obstetric trauma or pelvic surgery.

Obstetric Trauma

In developing countries, 90 percent of genitourinary fistulas arise from obstetric trauma, specifically from prolonged or obstructed labor (Arrowsmith, 1996). Their development in this setting reflects social customs and practices, lifestyle, or accepted obstetric management inherent to a particular society or geographic region (Meyer, 2007). For example, both childbearing at a young age, before the pelvis has developed or fully grown, and female circumcision, also termed *female genital mutilation* , may lead to a narrow vaginal introitus and can obstruct labor. Obstructed labor or malpresentation of the presenting fetal part can cause pressure or ischemic necrosis of the anterior vaginal wall and bladder, subsequently resulting in fistula formation. Alternatively, vaginal trauma may result from damage by instruments used to deliver stillborn infants or perform abortion. Malnutrition and limited health care in many of these countries further complicates wound healing. In contrast, in most developed countries, fistulas uncommonly follow obstetric procedures or deliveries. On rare occasion, cesarean deliveries, usually those accompanied by obstetric complications, have led to complex urinary fistulas (Billmeyer, 2001).

Pelvic Surgery

In developed countries, iatrogenic injury during pelvic surgery is responsible for 90 percent of vesicovaginal fistulas and the accepted incidence of fistula formation after pelvic surgery is 0.1 to 2 percent (Harris, 1995; Lee, 1988; Mattingly, 1978; Tancer, 1992). Eighty to 90 percent of genitourinary fistulas are related to surgery by obstetrician-gynecologists, whereas the remainder result from procedures performed by urologists and colorectal, vascular, and general surgeons. In industrialized countries, hysterectomy is the most common surgical cause of vesicovaginal fistula, accounting for approximately 75 percent of fistula cases (Symmonds, 1984). When all types of hysterectomy are included, vesicovaginal fistula is estimated to complicate 0.8 per 1,000 procedures (Harkki-Siren, 1998). Laparoscopic hysterectomies were associated with the greatest incidence (2 per 1,000), followed by abdominal (1 per 1,000), and vaginal (0.2 per 1,000) hysterectomies.

Because most genitourinary fistulas have an operative etiology, prevention and intraoperative recognition of lower urinary tract injury is imperative. Use of intraoperative cystoscopy has been shown to improve the detection rate of lower urinary tract injuries. Gilmour (1999) found in hysterectomies performed without cystoscopy, that ureteric and bladder injuries have crude occurrence rates of 1.6 and 2.6 per 1,000 procedures, respectively. With intraoperative cystoscopy, the detection rate of these injuries increased to 6.2 per 1,000 cases for ureteral injury and 10.4 per 1,000 cases for bladder injury. Thus, the implementation of routine cystoscopy may be a useful adjunct in the detection of lower urinary tract injury during hysterectomy. This in turn may ultimately result in a lower incidence of genitourinary fistula.

Other Causes

Although surgical and obstetric causes account for most urinary fistulas, other causes have been reported and include radiation therapy, malignancy, trauma, foreign bodies, infections, pelvic inflammation, and inflammatory bowel disease.

Radiation

Radiation therapy induces an endarteritis, which leads to tissue necrosis, and subsequent potential fistula formation. This modality is a frequent underlying cause and 6 percent of genitourinary fistulas are thought to result from radiation (Lee, 1988). Although most damage following radiation treatment develops within weeks and months, fistulas associated with radiation therapy may present up to 20 years after the original insult (Graham, 1967; Zoubek, 1989).

Malignancy

Tissue necrosis and deterioration is commonly associated with malignancy and may lead to urinary fistula formation. Emmert and Kohler (1996) found a 1.8-percent incidence of rectovaginal and vesicovaginal fistula in their analysis of nearly 2,100 women with cervical cancer. For this reason, tissue biopsy should routinely be performed in a woman with a fistula and history of malignancy.

Trauma and Foreign Body

Trauma sustained during sexual activity or sexual assault can result in genitourinary fistula formation and has been estimated to cause 4 percent of these defects (Kallol, 2002; Lee, 1988). Foreign bodies such as a neglected pessary, an aerosol cap, and vesical calculi are also documented agents (Binstock, 1990; Dalela, 2003; Grody, 1999).

Foreign bodies introduced during surgery such as collagen injected transurethrally and synthetic materials used in urethral sling procedures have also been reported (Kobashi, 1999; Pruthi, 2000). During sling surgeries, placement of the synthetic mesh under excess tension may contribute to increased tissue stress and necrosis. Accordingly, initial material selection and patient evaluation for risk factors of poor wound healing play important roles in fistula prevention (Giles, 2005). Materials that minimize the inflammatory foreign body reaction are preferred and will maximize biocompatibility. Ideally, a material should also be nontoxic, nonantigenic, and porous enough to admit immune and phagocytic cells and native tissue ingrowth (see Chap. 24, The Use of Mesh and Materials in Reconstructive Pelvic Surgery) (Birch, 2002).

Miscellaneous

Other rare causes of fistula formation include infections such as lymphogranuloma venereum, urinary tuberculosis, pelvic inflammation, and syphilis; inflammatory bowel disease; and autoimmune disease (Ba-Thike, 1992; Montiero, 1995). Moreover, conditions that interfere with healing, such as poorly controlled diabetes mellitus, smoking, local infection, peripheral vascular disease, chronic steroid use, and malignancy are risk factors.

Clinical Presentation

Vesicovaginal fistula classically presents with unexplained continuous urinary leakage from the vagina after a recent operation. Depending on the size and location of the fistula, the amount of urine will vary. Occasionally small-volume, intermittent leakage is mistaken for postoperative stress incontinence. For this reason, patients with new-onset urinary leakage should be examined thoroughly to exclude fistula formation. Other less specific symptoms of genitourinary fistula include fever, pain, ileus, and bladder irritability.

Vesicovaginal fistula may present days to weeks after the initial inciting surgery, and those following hysterectomy typically present at 1 to 3 weeks. Some fistulas, however, have longer latent periods and can cause symptoms a number of years later.

Diagnosis

HISTORY AND PHYSICAL EXAMINATION

A thorough history and physical examination identifies most cases of vesicovaginal fistula. Accordingly, historical information regarding obstetric deliveries, prior surgeries, previous management of fistula, and treatment of malignancy, especially involving pelvic surgery and radiation therapy, should be documented.

The physical examination is equally important, and often visual inspection during physical examination will identify the defect. A meticulous assessment for other fistulous tracts should be performed, and their location and size noted. Vaginoscopy has been described by some to improve fistula identification. For this evaluation, a laparoscope is inserted into a vagina, whose walls are held apart by a translucent plastic speculum (Andreoni, 2003).

During evaluation, it is mandatory to differentiate urinary leakage through a fistula (extraurethral leakage) from stress urinary incontinence (transurethral leakage). Moreover, occasionally the source of fluid present in the vagina is unclear and a small amount of urine can easily be mistaken for vaginal discharge. Measurement of the vaginal fluid's creatinine content, however, is an inexpensive test that may be used to confirm urine. Although levels of creatinine in urine can vary, with mean levels reaching 113.5 mg/dL, a value greater than 17 mg/dL is consistent with urine (Barr, 2005).

DYE INSTILLATION

Although the ideal method of confirming genitourinary fistula is by direct visualization, there are instances in which physical examination and inspection are unrevealing. In these circumstances, bladder instillation of visually distinct solutions such as methylene blue, sterile milk, or indigo carmine can often indicate the location.

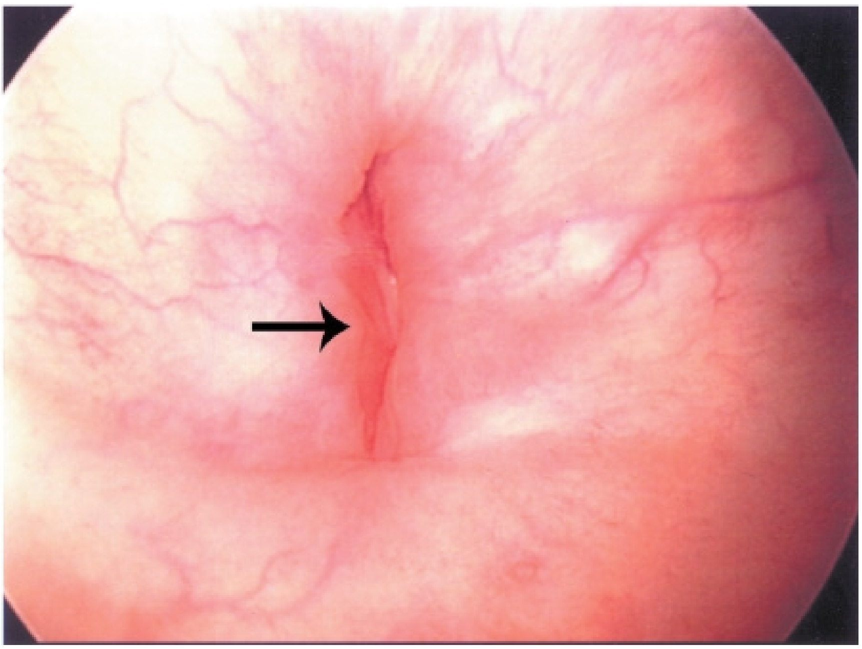
When the presence of a urinary fistula is uncertain, or the location in the vagina cannot be identified, a modified *tampon test* or

three-swab test is recommended (Moir, 1973). During testing, gauze is packed sequentially into the vaginal canal. A diluted solution of methylene blue or indigo carmine is instilled into the bladder in a retrograde fashion using a catheter. After the patient has engaged in 15 to 30 minutes of routine activity, the gauze is removed serially from the vagina and inspected for presence of dye. The specific gauze colored with dye suggests where in the vagina a fistulous tract is locatedâ€"a proximal or high location in the vagina for the innermost gauze, and a low or distal fistula for the outermost. If the distally placed sponge is stained with dye, however, it is important to confirm that it was not contaminated by stress incontinence.

CYSTOURETHROSCOPY

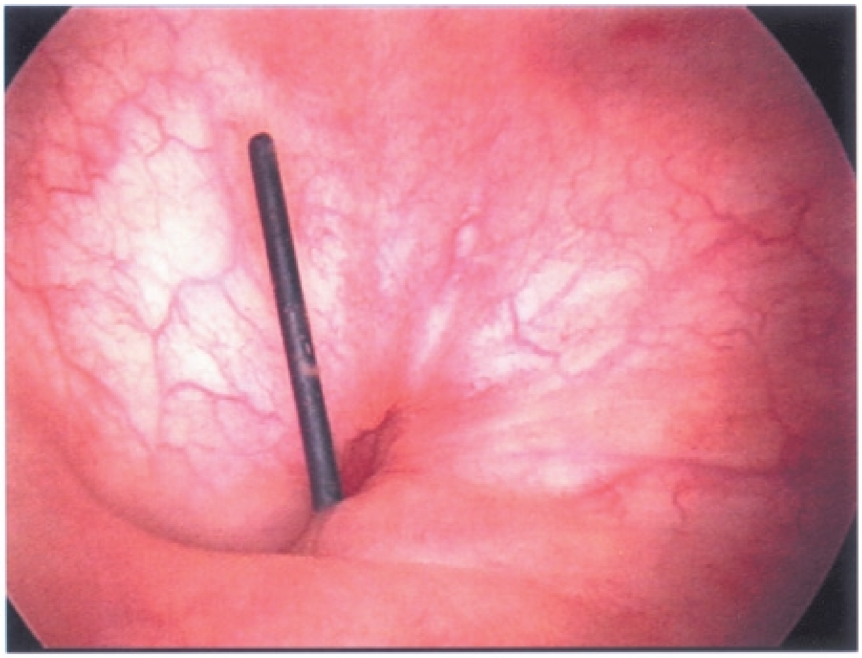
This form of endoscopy is another valuable adjunct to diagnostic evaluation (Fig. 26-1). It allows localization of the fistula, determination of its proximity to the ureteral orifices, and assessment of surrounding bladder mucosa viability. In addition, Andreoni and co-workers (2003) described the use of cystourethroscopy and vaginoscopy concurrently to identify vesicovaginal fisula.

FIGURE 26-1



A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

A. Cystoscopic view of vesicovaginal fistula **(arrow)** **B.** Probe placed through fistulous tract to facilitate cystoscopic visualization.

URETERAL INVOLVEMENT

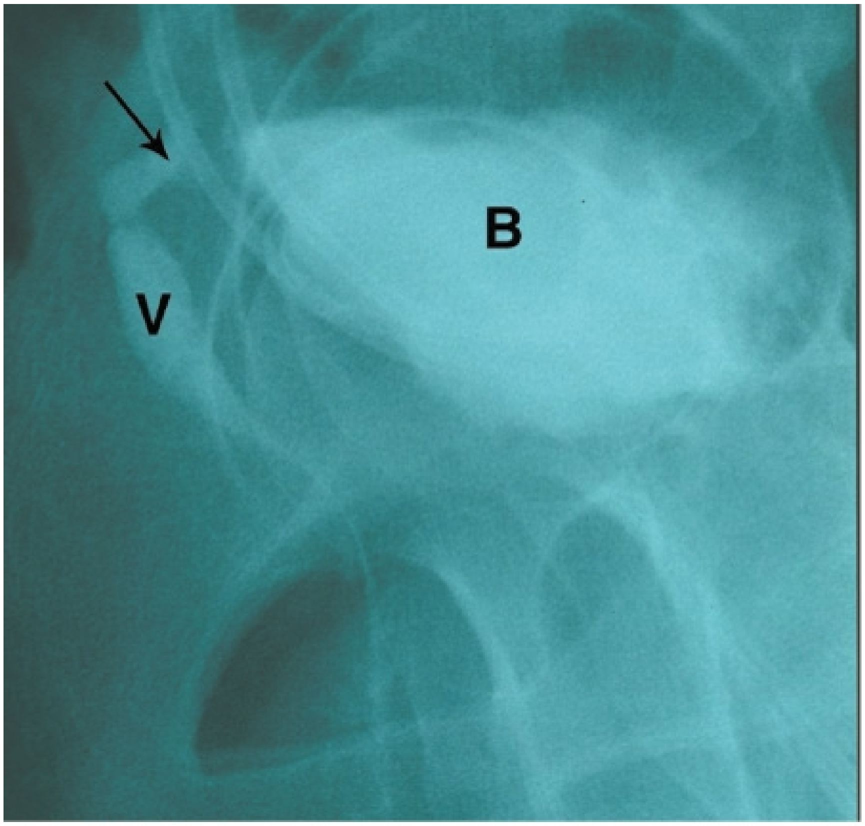
Concomitant ureteral involvement is estimated to complicate 10 to 15 percent of vesicovaginal fistulas and should be excluded in the diagnostic evaluation (Goodwin, 1980). Accordingly, intravenous urography is used to assess integrity of the upper collecting system and ureteral involvement in the fistula. Retrograde pyelography generally has the same diagnostic value as intravenous urography. However, some authors have attested to its higher diagnostic accuracy in detecting ureterovaginal fistulas (Dmochowski, 2002).

Alternatively, phenazopyridine hydrochloride (Pyridium, Warner Chilcott, Rockaway, NJ) can be used in conjunction with the three-swab test to determine if there is ureteral involvement. This agent is administered orally, is excreted renally, acts as a topical bladder analgesic, and as a side effect stains the urine orange. Women with suspected ureteral involvement are instructed to take a 200-mg oral dose a few hours before their clinic appointment. Gauze is packed serially into the vagina as described previously. If the most proximal (innermost) sponge is colored with orange dye, ureteral involvement is suspected. If both orange and blue dyes are seen, then both the bladder and ureter(*s*) are typically involved.

VOIDING CYSTOURETHROGRAPHY

This radiologic study can also demonstrate leakage into the vagina and help confirm the presence, location, and number of fistulous tracts (Fig. 26-2). Another radiographic tool that has been used to identify genitourinary fistula is sonography with color Doppler flow (Volkmer, 2000). The efficacy of this technique has not been substantiated, and some have documented low sensitivity rates for fistula detection (Adetiloye, 2000).

FIGURE 26-2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Voiding cystourethrogram of a vesicovaginal fistula. arrow = diverticulum; B = bladder; V = vagina.

Treatment

CONSERVATIVE TREATMENT

Occasionally, genitourinary fistulas may spontaneous close during continuous bladder drainage using an indwelling urinary catheter. Davits and Miranda (1991) described four cases of successful conservative management of vesicovaginal fistula with urinary catheter drainage ranging from 19 to 54 days. Additionally, Waaldjik (1994) found that 21 of 170 patients (12 percent) treated by catheterization alone had fistulas that healed spontaneously.

Data that correlate fistula size and success of conservative management, however, are limited. But generally, the larger the fistula, the less likely it is to heal without surgery. In 10 percent of cases, urinary fistulas close spontaneously after 2 to 8 weeks of transurethral catheterization, especially if the fistula is small (2 to 3 mm diameter) (Romics, 2002). In another series, small fistulas up to 2 cm in diameter spontaneously healed in 50 to 60 percent of patients treated with an indwelling catheter (Waaldijk, 1989). If the fistula has not closed within 4 weeks, however, it is unlikely to do so, probably secondary to collagen deposition and epithelialization of the fistulous tract (Bazi, 2007; Davits, 1991). Moreover, continued urinary drainage may lead to further inflammation and irritation of the bladder (Zimmern, 1991).

Fibrin sealant has been described for the treatment of vesicovaginal fistula. However, its use has been limited to an adjunctive capacity rather than primary surgical treatment (Evans, 2003). First, the data regarding the effectiveness of fibrin sealant are sparse, with a lack of well-designed trials. Secondly, compared with surgical treatment, fibrin sealant monotherapy has not been as durable and recurrence results (Kanaoka, 2001).

An attempt at conservative treatment is usually warranted. However, a balance between a conservative approach and a patient's desire for an expedited repair should be considered. The timing of intervention is dependent on achieving a compromise between reasonable conservative efforts and addressing the patient's immediate distress and quality of life. Indeed, most urinary fistulas ultimately require surgical intervention.

SURGICAL TREATMENT

General Principles

Although the first successful repair of a vesicovaginal fistula was reported hundreds of years ago, the fundamental principles of repair have withstood the test of time and result in a high cure rate with the first attempt at surgical repair. These fundamentals include appropriate pre- and intraoperative preparation; timely repair; multilayer, tension-free closure; assessment of adequate surrounding tissue viability; and postoperative bladder drainage.

Cure Rates

Surgical repair of genitourinary fistula is associated with high rates of cure (67 to 100 percent) (Dmochowski, 2002). Factors that affect this success rate include viability of the surrounding tissue, duration of the fistulous tract, prior irradiation, surgical technique, and surgeon experience. The first attempt at surgical repair is usually associated with the best chance of successful healing (Weed, 1978). Surgical repair of obstetric fistula has higher success rates, and 81 percent are corrected with the first attempt, and 65 percent with the second (Elkins, 1994; Hilton, 1998).

Timing of Repair

Traditional teaching recommends delayed repair of fistulas at 3 to 6 months after injury. However, this old dictum is probably no longer applicable. Most agree that unless there is severe infection or acute signs of inflammation, waiting is not necessary (Wein, 1980). Early surgical intervention of uncomplicated fistulas does not affect closure rates, yet appears to reduce social and psychological patient distress (Blaivas, 1995). Fistulas identified within the first 24 to 48 hours postoperatively can be safely repaired immediately with success rates of 90 to 100 percent (Blandy, 1991; Persky, 1979; Wang, 1990). Intervention should be individualized, balancing patient quality of life with viability of surrounding tissue.

Route of Surgical Repair

Although there are many different types of surgical repair for vesicovaginal fistula, data that support an optimal route are limited, and the lack of consensus may reflect the disparity in surgeon expertise and experience. Among important surgical considerations, ability to gain access to the fistula is essential and commonly dictates surgery selection. Fortunately, success rates are high whether the route of repair is transvaginal or transabdominal.

Vaginal

The transvaginal approach to genitourinary fistula repair is straightforward and direct. Compared with abdominal approaches, it is associated with shorter operative times, decreased blood loss, less morbidity, and shorter hospital stays (Wang, 1990). The transvaginal route also allows the use of ancillary equipment, such as ureteral stents. This is particularly useful if the fistula is located near ureteral orifices.

Latzko Technique

The *Latzko technique* has been likened to a partial colpocleisis (see Section 42-10, Vesicovaginal Fistula: Latzko Technique). Typically, it surgically apposes the most proximal portions of the anterior and posterior vaginal walls and thus partially obliterates the uppermost vagina. Since vaginal depth is potentially compromised, this technique is not an appropriate option if preservation of vaginal depth and retention of sexual function are desired.

Classical Technique

In contrast to the Latzko method, the *classical technique* involves excision of the fistulous tract. After excision of the fistula, the vaginal epithelium is undermined and widely mobilized. The bladder mucosa is closed, followed by subsequent closure of two layers of fibromuscular tissue. A watertight repair is confirmed and the vaginal epithelium is reapproximated.

Abdominal (Transperitoneal)

Difficult fistulas or those requiring supravesical urinary diversion require an abdominal approach (see Section 42-10, Vesicovaginal Fistula: Latzko Technique). The fistula is accessed through an intentional cystotomy. Similar to the transvaginal approach, the bladder and vaginal epithelia at the fistula site are undermined for approximately 1.5 cm in all directions. After adequate mobilization, the fistula site is closed in layers. This approach is used in situations in which: (1) the fistula is located proximally in a narrow vagina; (2) it is in close proximity to the ureteral orifices; (3) a concomitant ureteric fistula is present; (4) previous repairs of the fistula have been unsuccessful and the fistula is recurrent; (5) the vaginal walls are rigid with little mobility; (6) the fistula is large or complex in configuration; or (7) there is a need for an abdominal interposition graft.

Laparoscopic

Evidence-based support for laparoscopic genitourinary fistula repair has been limited to case reports and expert opinion (Das Mahapatra, 2007; Nezhat, 1994; Ou, 2004). The technique was first described in 1994 by Nezhat and requires advanced laparoscopic surgical skills. As a result, success with this approach appears to be highly dependent on surgeon expertise and experience.

Interpositional Flaps

Viability of the surrounding tissue is an important consideration in the repair of genitourinary fistula. When intervening tissues for fistula closure are weak and poorly vascularized, various tissue flaps may be placed vaginally or abdominally between the bladder and the vagina to lend support and blood supply (Eisen, 1974; Martius, 1928, Obrink, 1978; Patil, 1980; Sharma, 1980). Interposition flaps are useful in situations in which tissue viability is in question. However, their utility in uncomplicated cases of vesicovaginal fistula is unclear.

Urethrovaginal and Other Genitourinary Fistulas

Although vesicovaginal fistulas are the most common type of genitourinary fistula, other fistulas can exist and may be described based on their communication between anatomic structures. Urethrovaginal fistulas commonly result from surgery involving the anterior vaginal wall, in particular, anterior colporrhaphy and urethral diverticulectomy (Blaivas, 1989; Ganabathi, 1994a). As with vesicovaginal fistula, obstetric trauma remains the most common cause of urethrovaginal fistulas in developing countries. Here, prolonged labor with ensuing tissue necrosis results in development of fistulas. Frequently, patients present with continuous urinary drainage into the vagina or with stress urinary incontinence. The principles of repair are similar: layered closure, tension-free repair, and postoperative bladder drainage. Other types of genitourinary fistula can also occur (see Table 26-1).

URETHRAL DIVERTICULUM

A urethral diverticulum is a cystic enlargement of a paraurethral gland, which is found in the anterior vaginal wall and communicates directly with the urethra (Fig. 26-3). Often fluid filled, this outpouching of the urethra is commonly asymptomatic and frequently diagnosed incidentally on routine examination. However, many present with symptoms and often require surgical excision.

FIGURE 26-3

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Transurethral expression of discharge with compression of urethral diverticulum seen in anterior vaginal wall.

Incidence

Urethral diverticulum is reported to develop in 1 to 5 percent of the general female population and because of greater awareness and radiologic advances, rates of diagnosis are increasing (Dmochowski, 2002). This incidence may be an underestimation of the true incidence because diverticula are frequently asymptomatic, and thus underreported. However, in women with lower urinary tract symptoms, the incidence dramatically increases and may reach 40 percent (Stewart, 1981).

Urethral diverticulum may be found in any age group, but is diagnosed most often in the third to sixth decades of life and more commonly in females than in males (Aldridge, 1978). Although some authors have reported a 6:1 predominance of urethral diverticula in African-Americans compared with Caucasians, others have found no racial predisposition for the condition (Davis, 1970; Leach, 1987).

Etiology and Pathophysiology

CONGENITAL DIVERTICULUM

The etiology of urethral diverticula is unclear. Although most are thought to be acquired, diverticula of congenital origin have been reported (Bhatnagar, 1999; Nel, 1955). Congenital causes of urethral diverticula include persistence of embryologic remnants, defective closure of the ventral portion of the urethra, and congenital cystic dilatation of paraurethral glands (Ratner, 1949).

An appreciation of the embryology and anatomy of the female genital tract and surrounding structures contributes, in part, to our

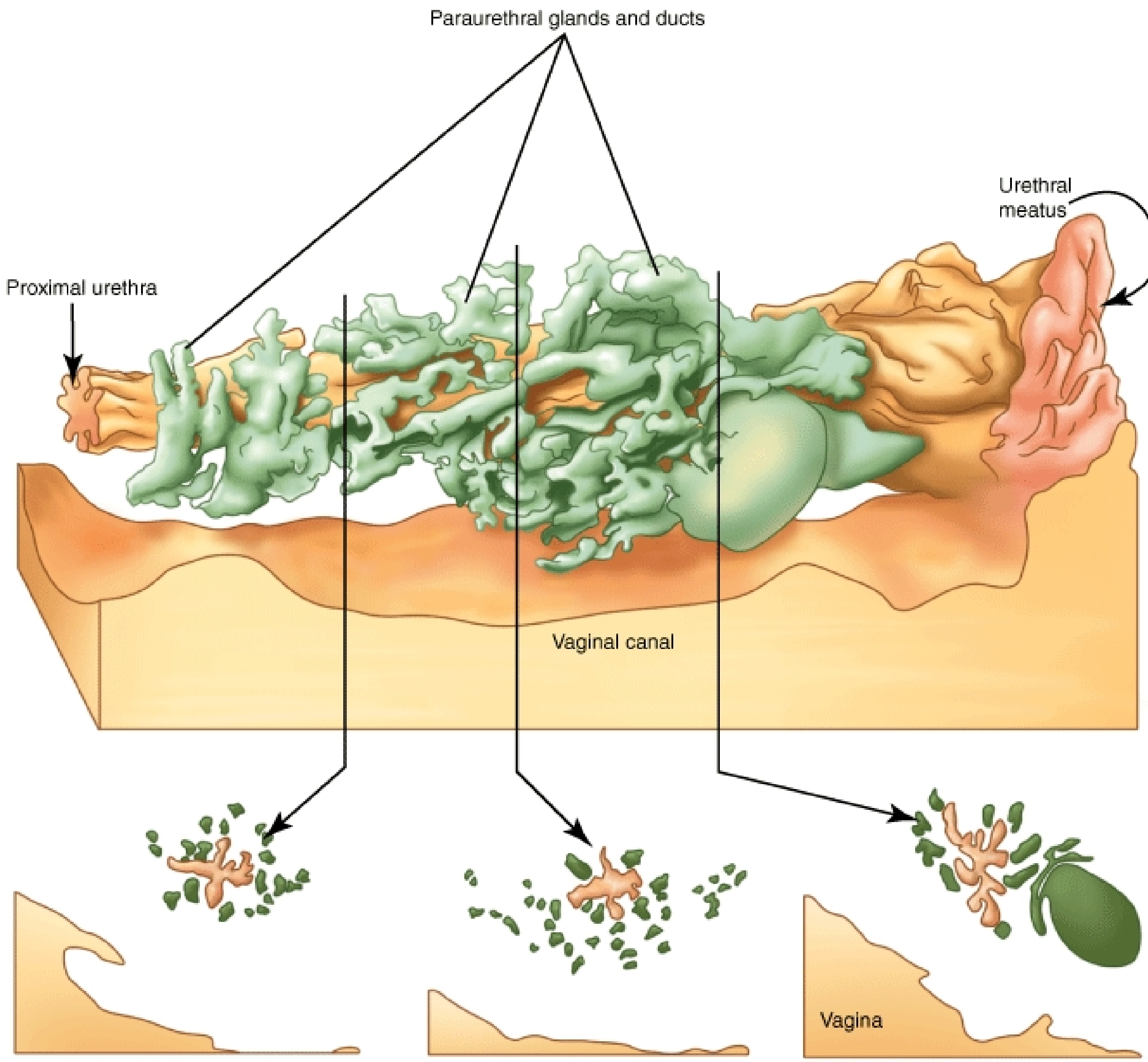
understanding of congenital urethral diverticulum. During development of the vagina, the caudal aspect of the paired mÃ¼llerian tubes fuses with an evagination of the urogenital sinus. The mÃ¼llerian tubes form the upper vagina, whereas the urogenital sinus gives rise to the distal vagina and vestibule (see Fig. 18-4). In the vagina, mÃ¼llerian mucinous columnar epithelium is replaced by squamous epithelium of the urogenital sinus. Similarly, the epithelium of the female urethra is also derived from the urogenital sinus. When the process of epithelial replacement is arrested, small foci of mÃ¼llerian epithelium may persist and may form cysts or diverticula.

ACQUIRED DIVERTICULUM

More commonly, diverticula are acquired and may result from infection, birth trauma, and traumatic instrumentation.

The most widely held theory regarding urethral diverticular development dates back to Routh (1890) and involves the paraurethral glands and their ducts. The paraurethral glands surround and cluster most densely along the urethra's inferolateral border (Fig. 26-4). Of these glands, the Skene glands are the most distal and typically the largest. The paraurethral glands connect to the urethral canal via a network of branching ducts. The arborizing pattern in portions of this network helps to explain the complexity of some urethral diverticula (Vakili, 2003).

FIGURE 26-4

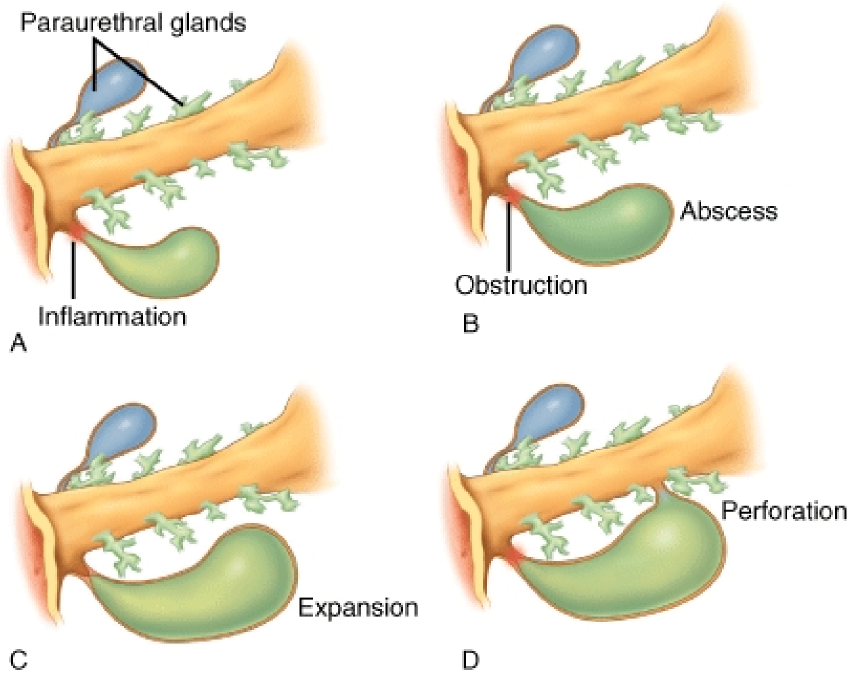


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Complex configuration of paraurethral glands. (*From Huffman, 1948, with permission* .)

Routh theorized that infection and inflammation obstructs these ducts, leading to cystic dilation. If intervention is not instituted promptly, abscess formation may ensue. Subsequent abscess progression and continued inflammation can lead to submural rupture of the gland into the urethral lumen, creating a communication between the two (Fig. 26-5). As the infection clears, the dilated diverticular sac and communicating ostium into the urethra persist. Of infectious agents, *Neisseria gonorrhoeae* and *Chlamydia trachomatis* are organisms commonly associated with urethritis and severe inflammation of the paraurethral glands.

FIGURE 26-5



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Mechanism of urethral diverticulum development. (*From Elkins, 1999, with permission* .)

In addition to infection, damage to urethral tissue may lead to tissue swelling and paraurethral duct obstruction. Accordingly, urethral trauma sustained during childbirth and during urethral instrumentation has been suggested as an etiology (McNally, 1935). Moreover, different social customs and obstetric practices in the developing world can potentially contribute to urethra trauma and diverticulum development. Obstetric trauma may result from delivery at an early age, prolonged labor, and vaginal trauma during delivery. However, Pathak and House (1970) found that 40 percent of urethral diverticula in their series developed in nulliparous women, suggesting that causes in addition to childbirth are associated. For example, female genital mutilation or repeated urethral dilatations may result in urethral trauma.

Calculi

Stones may develop within large diverticulum, and the reported frequency approximates 10 percent (Perlmutter, 1993). Stones may be singular or multiple and are usually composed of calcium oxalate or calcium phosphate. Stagnation of urine and precipitation of salts within the diverticular sac lead to crystal and subsequent stone formation.

Cancer

Malignant transformation within a urethral diverticulum is rare and accounts for only 5 percent of urethral cancer. Although most of these tumors are adenocarcinomas, transitional cell and squamous cell carcinomas have also been identified (Clayton, 1992; Young, 2007). These tumors typically are found in women in their 60s or 70s. Although hematuria and irritative voiding complaints are common, palpation of a periurethral mass and urinary obstructive symptoms should prompt biopsy (Ghoniem, 2004). Because fewer than 100 cases of urethral cancer associated with urethral diverticula have been reported, development of definitive treatment strategies has been limited. Currently, these cancers are treated by anterior exenteration or by diverticulectomy, alone or with adjuvant radiation therapy (Shalev, 2002).

Classification

Early classification systems organized urethral diverticula according to their radiographic complexity and described them as: (1) simple saccular, (2) multiple, or (3) compound or complex with branching sinuses (Lang, 1959). Alternatively, to standardize surgical treatment, Ginsburg and Genadry (1983) created a preoperative classification system based on urethral location. This system organizes diverticula depending on their urethral location and describes lesions as type 1 (proximal third), type 2 (middle third), and type 3 (distal third).

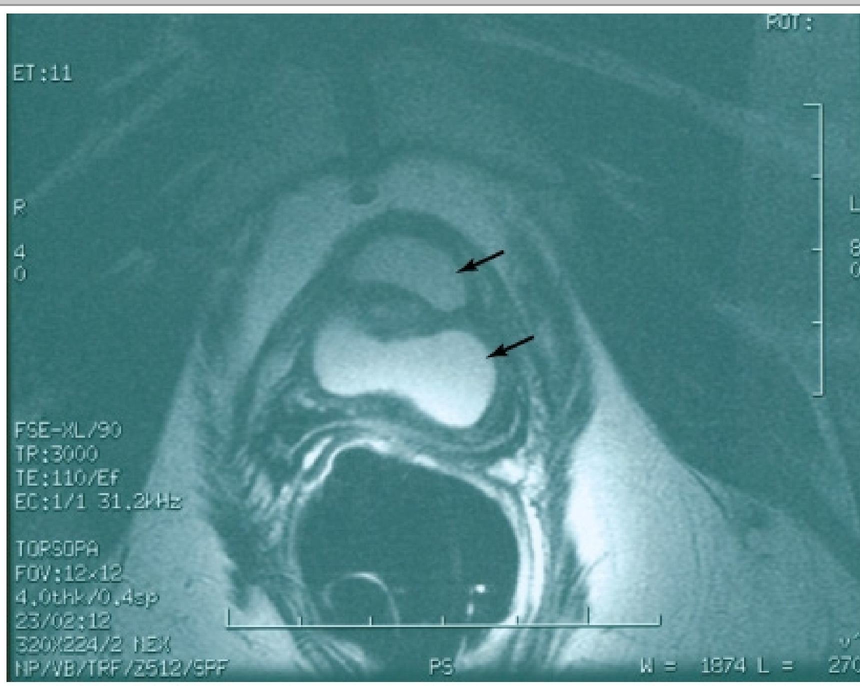
In an attempt to fully incorporate all characteristics necessary to adequately assign treatment, Leach and co-workers (1993) constructed the L/N/S/C3 classification system. In this system, the characteristics of a diverticulum are described according to its location (L), number (N), size (S), and communication, configuration, and continence status of the patient (C3).

Assigning location to these lesions is important in determining if certain surgical techniques, such as marsupialization, are feasible. Location is described in relation to the urethra and is defined as distal, mid-, or proximal urethral, and as with or without extension beneath the bladder neck. In their series of 61 patients, these investigators found that most were in the midurethra (62 percent). Logically, this distribution reflects the predominance of paraurethral glands along the middle third of the urethra.

In addition to location, the number of diverticula is an important determination preoperatively. Inadequate excision and symptom persistence may follow a failure to identify multiple diverticula. Diverticulum size is measured in centimeters and similarly may influence treatment options. For example, some authors recommend concomitant interpositional tissue flaps for large diverticula (Dmochowski, 2002). Moreover, urinary incontinence may develop de novo or persist if the diverticulum is extremely large and involves sphincter continence mechanisms.

The configuration of the diverticula may be described as solitary or multiloculated and as simple, saddle-shaped, or circumferential (Fig. 26-6). Preoperative knowledge regarding configuration can aid in complete surgical excision and allows for interpositional flap preparation for those cases requiring extensive urethral resection (Rovner, 2003).

FIGURE 26-6



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Magnetic resonance image of a circumferential urethral diverticulum. **Arrows** show diverticulum extending around the urethra.

Obviously, successful repair of the urethral wall defect depends in great part on identifying the opening of the diverticulum into the

urethral canal. Preoperative determination of the communication site is thus important, with ostia being classified as proximal, mid-, or distal urethral. Leach and his associates found mid-urethral communication sites to be the most common (60 percent), followed by proximal (25 percent) and distal (15 percent) urethral sites.

Finally, in this classification system, the continence status and urethral hypermobility of the patient is documented. Almost half of the patients in their series had stress urinary incontinence, and these authors suggest that the presence of urethral hypermobility is an indication for concomitant anti-incontinence surgery. Although several studies have documented the safety of performing concurrent bladder-neck suspension, this approach is still considered by some as controversial due to concerns of urethral erosion following suspension (Bass, 1991; Faerber, 1998; Ganabathi, 1994b).

Although there is no universal consensus on this issue, it seems reasonable to treat the diverticulum first and then to consider anti-incontinence surgery if urinary incontinence persists. Pursuing treatment in this staged fashion is a particularly realistic option because of the current armamentarium of minimally invasive surgical procedures for the treatment of urinary incontinence, such as midurethral slings.

Patient Signs and Symptoms

Urethral diverticula are frequently asymptomatic and discovered incidentally on gynecologic or urologic examination for other complaints. However, when symptomatic, their presentations may vary and reflect their characteristics, especially size, location, and extension. Postvoid dribbling and egress of discharge through the urethra with compression of a suburethral mass are pathognomonic. However, few women present so classically. For most patients, symptoms are nonspecific and include pain, dyspareunia, and a number of urinary symptoms. In a retrospective review, Romanzi and colleagues (2000) found that pain was one of the most common symptoms reported (48 percent). Pain is thought to result from occlusion of the diverticular neck and cystic dilatation behind the obstruction. In addition, dyspareunia may develop if the diverticulum is sufficiently large, inflamed, or infected. Accordingly, women may note either entry or deep dyspareunia, depending on whether the diverticulum is distal or proximal.

A large diverticulum can often be mistaken for early-stage pelvic organ prolapse, especially when the presenting complaint is vaginal fullness, bulge, or pressure. In these cases, the palpable vaginal mass caused by a diverticulum may be mistaken for a cystocele or rectocele. Careful systematic palpation of the vaginal wall will distinguish prolapse from a discrete vaginal wall cyst or diverticulum in most cases.

A variety of lower urinary tract symptoms are commonly associated with urethral diverticulum. Specifically, urinary incontinence is noted by 35 to 60 percent of affected women. This typically results from involvement of the diverticulum with the continence mechanism or with support of the urethrovesical junction (see Chap. 23, Continence) (Romanzi, 2000; Ganabathi, 1994b). In addition, during micturition, urine may enter the diverticular sac, only to later spill from the sac and present as postvoid dribble or as urinary incontinence. Urinary retention has also been reported to complicate diverticula (Nitti, 1999). Because symptoms of retention frequently accompany cancers growing within a diverticulum or around the urethra, women with urinary retention and an associated periurethral or urethral induration require biopsy to exclude malignancy (von Pechmann, 2003).

Infection commonly complicates urethral diverticulum. In their treatment of 18 women with diverticula, Fortunato and associates (2001) noted acute cystitis in eight, dysuria in seven, and recurrent cystitis in 11.

Diagnosis

For many women, urethral diverticula may be diagnosed using simply a detailed history, physical examination, and high index of suspicion. Patient history should focus on the common characteristics and symptoms of diverticula noted earlier. In addition, a history of prior vaginal trauma, infections, or surgery should be sought. However, despite available clinical and radiologic tools, the diagnosis for many women is delayed, as women may be treated for stress or urge incontinence, chronic cystitis, trigonitis, urethral syndrome, vulvovestibulitis, cystocele, and idiopathic chronic pelvic pain prior to identification of a diverticulum (Romanzi, 2000). Moreover, the diverticulum itself may mimic a Gartner duct cyst, vaginal inclusion cyst, ectopic ureterocele, or endometrioma (Chowdhry, 2004).

PHYSICAL EXAMINATION

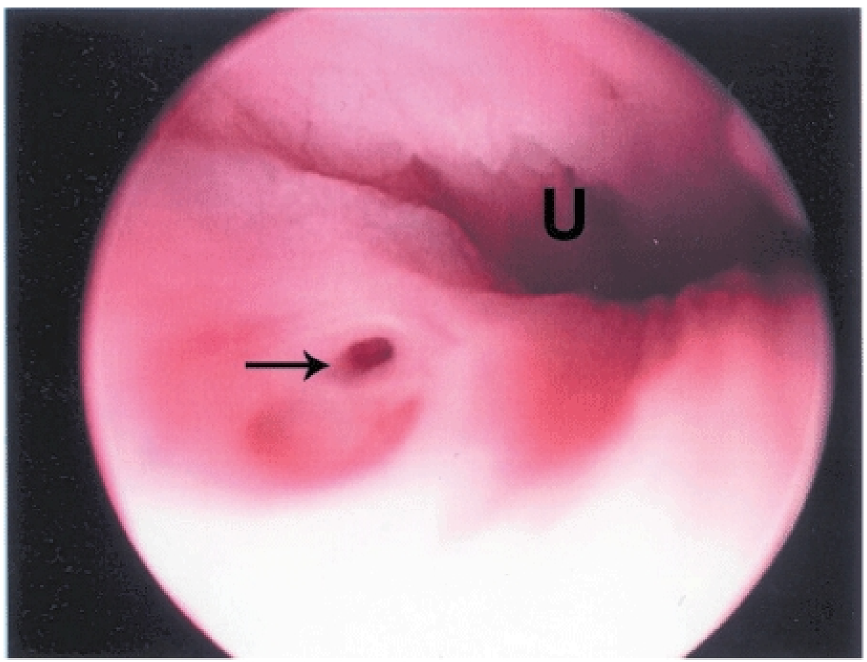
On examination, the most common finding is an anterior vaginal mass underlying the urethra and is detected in 50 to 90 percent of symptomatic patients. (Ganabathi, 1994b; Gerrard, 2003; Romanzi, 2000). Although urethral expression of purulent material with compression of the mass is common, failure to demonstrate transurethral expression of discharge does not exclude the diagnosis. Stenosis of the diverticular duct may obstruct sac emptying in these cases. Meticulous examination and palpation should be performed along the entire course of the urethra. Once diverticula are identified, their size, borders, consistency, and number should be determined.

However, when physical examination alone precludes complete delineation of these characteristics, further diagnostic testing may be required. The diagnosis of urethral diverticulum has increased in the past few decades due to improved diagnostic modalities. Of available tests, each has significant advantages and disadvantages. For this reason, investigators may disagree as to which should be chosen primarily in evaluation of urethral diverticula. Accordingly, clinicians should be familiar with the each modality's strengths and select whichever best fits the clinical setting.

CYSTOURETHROSCOPY

Of the diagnostic procedures used to detect urethral diverticula, cystourethroscopy is the only modality that allows direct inspection of the urethra and bladder. During cystourethroscopy, fingers pressed upward against the anterior vaginal wall occlude the bladder neck and allow the distending medium to create positive pressure and open diverticular ostia (Fig. 26-7). Use of a zero-degree cystoscopic lens allows complete assessment of the urethra, aiding direct visualization of diverticular ostia and a display of purulent discharge from them.

FIGURE 26-7



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Diverticular opening visualized on cystourethroscopic examination (arrow). U = urethra.

A primary advantage to cystourethroscopy includes its accuracy in diverticula detection (Summitt, 1992). In addition, many women with diverticula present with nonspecific lower urinary tract symptoms and endoscopic evaluation of the urethra and bladder allow exclusion of other etiologies for these symptoms such as urethritis, cystitis, stones, or stenosis. Despite these advantages and its common use by urogynecologists, cystourethroscopy is used less frequently by gynecologic generalists, because of the cystoscopic expertise and general knowledge of bladder and urethral mucosal anatomy it requires. Even for clinicians who are experienced with

cystourethroscopy, this tool may still fail to display all diverticula. For example, a poor seal between the cystoscope and distal urethral muscosa may lead to inadequate distension and failure to identify distally located diverticula. Moreover, those whose ostia are stenotic, and thus do not communicate with the urethral lumen, may be missed. Cystourethroscopy is minimally invasive, and patient pain and risk of postprocedural infection are also legitimate concerns. Lastly, important information regarding size, consistency, and circumferential extent of the diverticulum may not be obtained with this tool.

VOIDING CYSTOURETHROGRAM

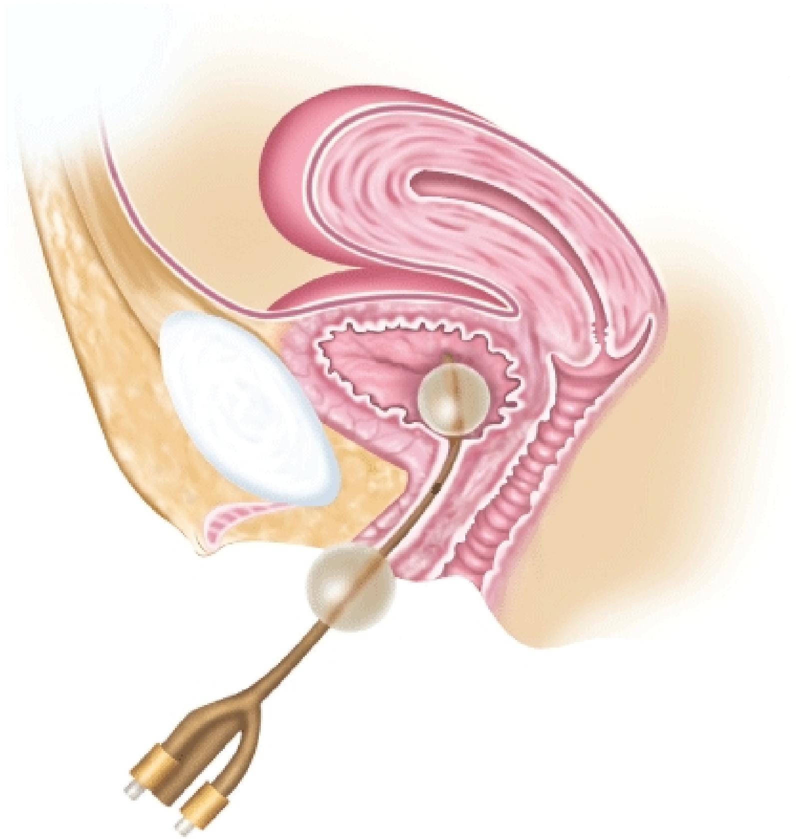
Voiding cystourethrogram (VCUG) is used by many as an initial tool in the evaluation of urethral diverticulum. Radiographic contrast instilled into the bladder will fill the diverticular sac during voiding and postvoid radiographs display the diverticulum.

Although this test is painless and simple to perform, its overall reported accuracy approximates only 65 percent, and thus many prefer positive-pressure urethrography as a primary diagnostic tool (O'Shaughnessy, 2006). Additionally, VCUG involves exposing the patient to ionizing radiation, albeit minimal.

POSITIVE-PRESSURE URETHROGRAPHY

Following its introduction by Davis and Cian (1956), positive-pressure urethrography (PPUG) dramatically improved the detection of urethral diverticula, and at that time rapidly became the standard of care. During PPUG, a double-balloon, triple-lumen catheter is inserted through the urethra, and its tip enters the bladder (Fig. 26-8) (Trattner catheter, CR Bard, Inc., Murray Hill, NJ). Inflating the proximal balloon allows it to be pulled snug against and occlude the urethra at the urethrovesical junction. The distal balloon obstructs the distal urethra. A single catheter port between the two balloons allows instillation of radiopaque contrast dye, subsequent distension of the urethra, and expansion of the diverticulum under positive pressure.

FIGURE 26-8



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

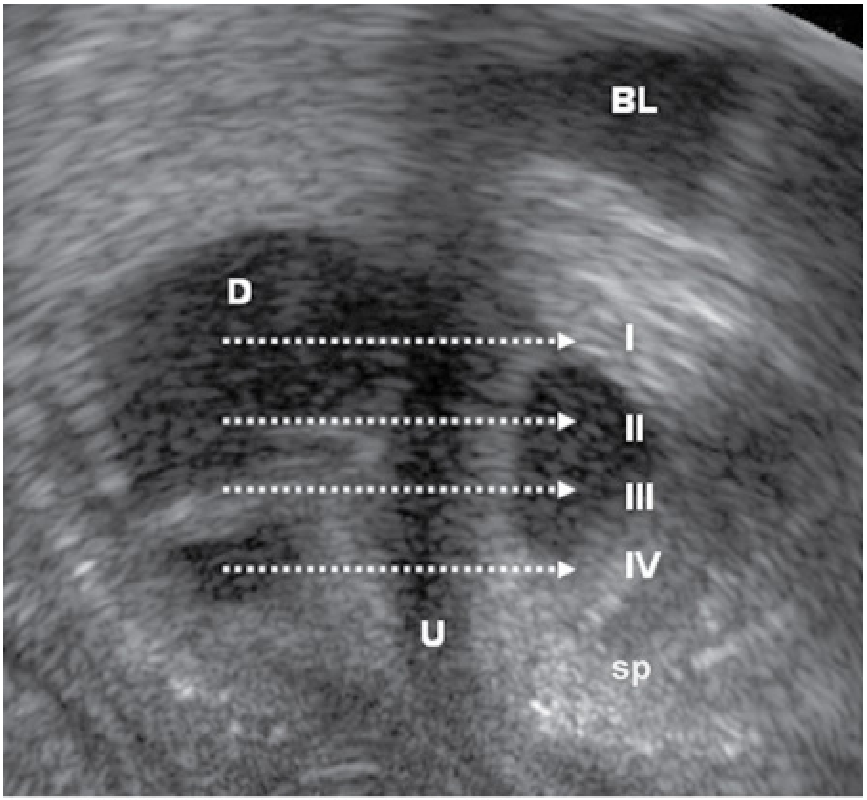
Trattner double-balloon catheter used to diagnose urethral diverticula. (*From Greenberg, 1981, with permission.*)

Urethrography is an effective modality for accurately identifying diverticula, and its sensitivity surpasses that of VCUG (Jacoby, 1999; Wang, 2000). Golomb and colleagues (2003) in their small series found a 100-percent sensitivity with PPUG compared with 66 percent for VCUG. In every case in their study, PPUG defined the location, size, configuration, and communication of the diverticula to the urethra. However, PPUG can be time-consuming, technically difficult, and associated with patient discomfort and risk of postprocedural infection. Moreover, similarly to VCUG, diverticula may be missed if thick pus or debris prevents adequate filling with contrast medium or if the ostium is obstructed and prevents communication with the urethral lumen. Accordingly, although PPUG for many has been a primary tool for diagnosing urethral diverticula, it has gradually been replaced by other radiologic modalities due to the lack of necessary equipment and expertise and because of its associated patient discomfort and invasiveness.

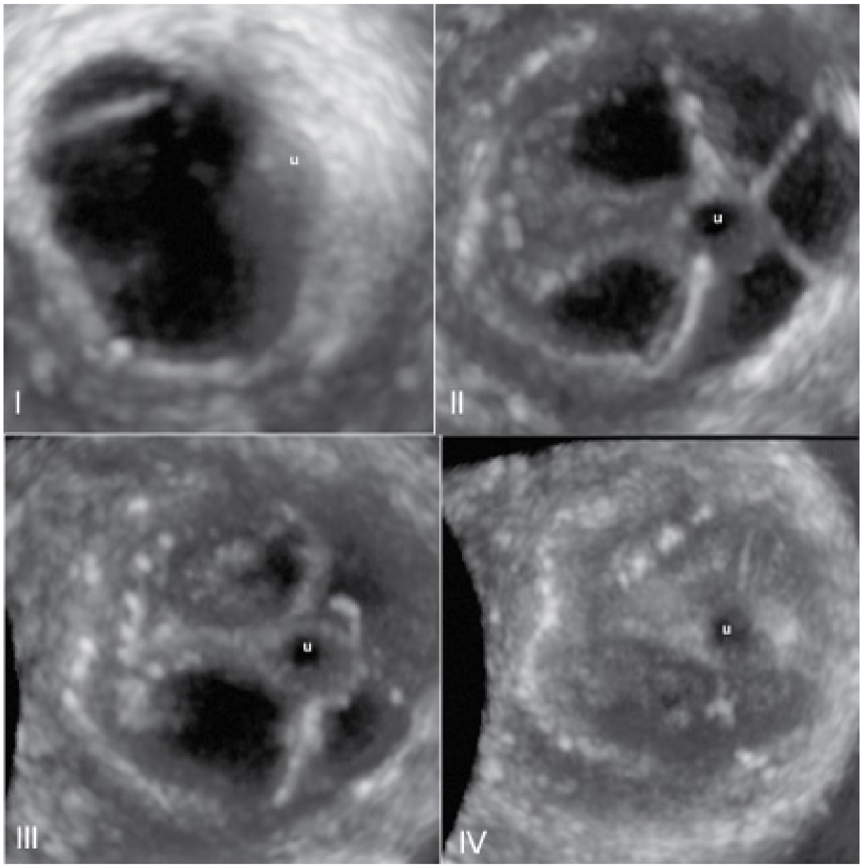
SONOGRAPHY

This tool is a relatively new modality used to evaluate urethral diverticula, and has been shown to be effective (Gerrard, 2003). Suggested technical advantages of sonography in this setting include visualization of diverticula that did not fill during radiographic contrast studies and characterization of diverticular wall thickness, size, and internal architecture (Fig. 26-9) (Yang, 2005). In addition, Siegel and co-workers (1998) noted that sonography provided information on other lesions such as periurethral leiomyomas, diffuse urethritis, and periurethral scarring. Transabdominal, -vaginal, -rectal, -perineal, and urethral sonography have all been reported (Keefe, 1991; Vargas-Serrano, 1997). Although the advantages of sonography include patient comfort, avoidance of ionizing radiation and contrast exposure, relative low cost, and reduced invasiveness, its role in the diagnosis of urethral diverticula has not been clearly established. It remains an academic or adjunctive technique for now.

FIGURE 26-9



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Transvaginal ultrasonographic view of urethral diverticula. sonographic view of a urethral diverticulum. The top image is a sagittal scan displaying the urethra and diverticulum. Dotted lines labeled with Roman numerals reflect the urethral level at which the remaining four axial views were obtained. D = diverticulum; sp = symphysis pubis; U = urethra. *(From Yang, 2005, with permission.)*

MAGNETIC RESONANCE IMAGING

Within the last decade, the use of magnetic resonance (MR) imaging has become more common in the diagnosis of periurethral pathology, and is particularly useful in establishing the location, extent, and internal characteristics of periurethral masses (Kim, 1993; Nurenberg, 1997). For this reason, MR imaging is often recommended when diverticular architecture is complex, and its entire extent has not been delineated by other modalities (Daneshgari, 1999; Rovner, 2003; Vakili, 2003). In comparison with other imaging modalities, MR imaging has shown comparable or superior sensitivity for detecting urethral diverticula (Lorenzo, 2003; Neitlich, 1998). To improve image resolution, MR imaging may be used in conjunction with an imaging coil placed in the rectum or vagina. The coil, which is housed inside a probe, improves the image quality of structures surrounding the rectum or vagina (Blander, 2001). In spite of the advantages of MR imaging, procedure costs should be considered within the clinical context. For solitary diverticula with clearly demarcated boundaries and without extension, costly and extensive imaging is not necessary.

Because there is still no consensus on which modality should be used primarily, it is reasonable to begin with cystourethroscopic evaluation followed by VCUG. If the initial evaluation is unrevealing but the diagnostic suspicion remains high, then MR imaging with an endorectal coil may be informative.

Treatment

OBSERVATION

Many women with minimal or no symptoms may decline surgery due to its associated risks of urethrovaginal fistula and sphincter

defect incontinence. Long-term data on these women regarding rates of subsequent symptom development, diverticulum enlargement, and eventual need for surgical excision, however, are lacking.

SURGICAL

For many women, especially those with persistent symptoms, surgical correction is often indicated and procedures include diverticulectomy, marsupialization, and transvaginal partial ablation.

Of these procedures, diverticulectomy is the most commonly used and can be selected to treat diverticula at any site along the urethra (see Section 42-9, Urethral Diverticulum Repair). Vaginal excision of the entire diverticulum provides long-term correction of the urethral defect, normal urine stream, and high rates of postoperative continence. Disadvantages, however, include the risk of postsurgical urethral stenosis, urethrovaginal fistula, and potential injury of the urinary sphincter continence mechanism (Ljungqvist, 2007).

Alternatively, marsupialization of the diverticulum, also known as the Spence procedure, may be chosen to correct distal diverticula (Spence, 1970). The procedure is a meatotomy that when healed forms a new urethral meatus. Although simple to perform, this procedure alters the configuration of the meatus, and women often note a spray pattern with urination.

For proximal diverticula, partial ablation of the diverticular sac may be preferred to avoid the risk of bladder entry or bladder neck injury, which is associated with sacs in this location. Tancer and colleagues (1983) described this procedure, during which excess diverticular wall is excised vaginally, the diverticular neck is not removed, but remaining diverticular wall tissue is reapproximated to close the defect.

In addition to these approaches, case reports have described other procedures such as urethroscopic transurethral electrosurgical fulguration of the diverticular sac and transurethral incision to widen the diverticular ostia (Miskowiak, 1989; Saito, 2000; Vergunst, 1996). Data regarding long-term efficacy and complication rates with these techniques, however, are lacking.

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PRINCIPLES OF CHEMOTHERAPY: INTRODUCTION

For the past 50 years, the incorporation of chemotherapy into the treatment of gynecologic cancers has been in a state of perpetual evolution. New advances develop frequently and pose a continual challenge to stay current in the field. Thus, a foundation for navigating the terminology of this important third component of cancer treatment is essential.

BIOLOGY OF CANCER GROWTH

In principle, drugs are able to treat cancer and spare normal cells by exploiting inherent differences in their individual growth patterns. Each tumor type has its own characteristics, which explains why the same chemotherapy regimen is not equally effective for the whole spectrum of gynecologic cancers. Selecting appropriate drugs and limiting the toxicity demands an understanding of the fundamentals of cellular kinetics.

The Cell Cycle

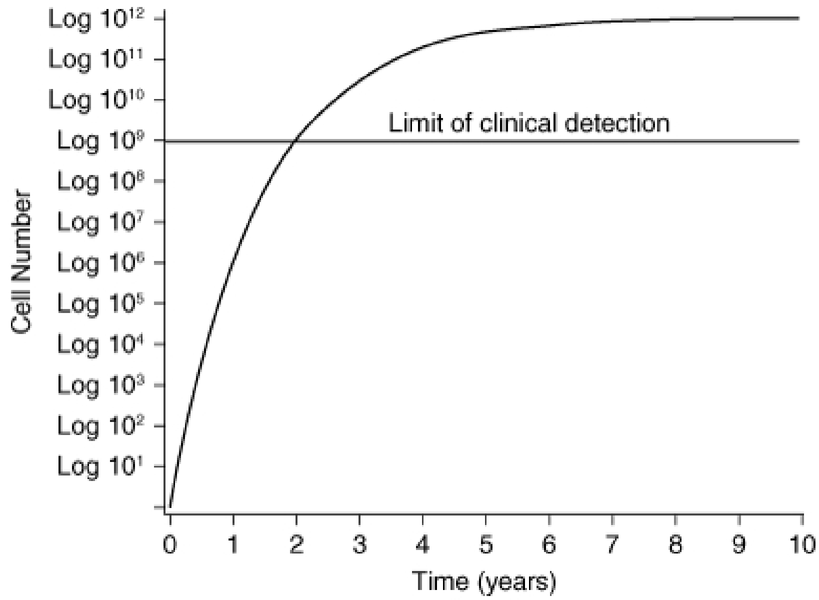
All dividing cells follow the same basic sequence for replication. The *cell generation time* is the length of time required to complete the five phases of the cell cycle (Fig. 28-8). The G_1 phase (G stands for gap) involves various cellular activities, such as protein synthesis, RNA synthesis, and DNA repair. When prolonged, the cell is considered to be in the G_0 , or resting, phase. G_1 cells may either terminally differentiate into the G_0 phase or re-enter the cell cycle after a period of quiescence. During the S phase, new DNA synthesis occurs. The G_2 (premitotic) phase is characterized by cells having twice the DNA content as they prepare for division. Finally, actual mitosis and chromosomal division takes place during the M phase.

Tumors *do not* have faster generation times, but instead have many more cells in the active phases of replication. In contrast, normal tissues have a much larger number of cells in the G_0 phase. As a result, cancer cells proceeding through the cell cycle are highly sensitive to chemotherapeutic agents, whereas normal cells in G_0 are protected. This growth pattern disparity underlies the effectiveness of chemotherapeutic agents.

Cancer Cell Growth

Tumors are characterized by a *gompertzian growth* pattern (Fig. 27-1). Fundamentally, a tumor mass requires progressively longer times to double in size as it enlarges. When a cancer is microscopic and nonpalpable, growth is exponential. However, as a tumor enlarges, the number of its cells undergoing replication decreases.

FIGURE 27-1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

The gompertzian growth curve. During early stages of tumor expansion, growth is exponential, but with enlargement, tumor growth slows. Consequently, most tumors have completed their exponential growth phase at the time of clinical detection.

When tumors are in the exponential phase of gompertzian growth, they should be more sensitive to chemotherapy because a larger percentage of cells are in the active phase of the cell cycle. For this reason, metastases should be more sensitive to chemotherapy than a primary tumor. To take advantage of this potential benefit, advanced ovarian cancer is usually treated with surgical debulking and adjuvant chemotherapy. In addition, when a tumor mass shrinks in response to treatment, the presumption is that a greater number of cells will enter the active phase of the cell cycle to accelerate growth. This larger percentage of replicating cells should also increase the sensitivity of a tumor to chemotherapy.

Doubling Time

The time that it takes for a tumor to double in size is commonly referred to as its *doubling time.* Whereas the cell cycle generally refers to the activity of individual tumor cells, doubling time refers to the growth of an entire heterogenous tumor mass. In humans, the doubling times of specific tumors vary greatly.

The speed with which tumors grow and double in size is largely regulated by the number of cells that are actively dividing, known as the *growth fraction.* Typically, only a small percentage of the tumor will have cells that are rapidly proliferating. The remaining cells are in the G_0 resting phase. In general, tumors that are cured by chemotherapy are those with a high growth fraction, such as gestational trophoblastic neoplasia. When tumor volume is reduced by surgery or chemotherapy, the remaining tumor cells are theoretically propelled from the G_0 phase into the more vulnerable phases of the cell cycle, rendering them susceptible to chemotherapy.

Cell Kinetics

Chemotherapeutic agents work by first-order kinetics to kill a constant *fraction* of cells rather than a constant number. For example, one dose of a cytotoxic drug may result in a few logs (10^2 to 10^4) of cell kill, but not lead to a cure since tumor burden may be 10^{12} cells or more. Thus, the magnitude of cell kill necessary to eradicate a tumor typically requires intermittent courses of chemotherapy with more than one drug. Furthermore, first-order kinetics provides a rationale for surgical removal of large volume disease, followed by adjuvant chemotherapy to kill small tumor implants that contain 10^1 to 10^4 cells. In general, a cancer's

curability is inversely proportional to the number of viable tumor cells at the beginning of chemotherapy.

Some drugs achieve cell kill at several phases of the cell cycle. These *cell cycleâ€"nonspecific* agents, such as alkylating drugs, act in all phases of replication from G_0 to the M phase. *Cell cycleâ€"specific* agents act only on cells that are in a specific phase. By combining drugs that act in different phases of the cell cycle, the overall cell kill should be enhanced.

CLINICAL USE OF CHEMOTHERAPY

Clinical Setting

Chemotherapy may be used in four different ways (Table 27-1). The term *induction chemotherapy* is defined as primary treatment for patients with an advanced malignancy when no feasible alternative treatment exists. *Adjuvant chemotherapy* describes systemic treatment after a primary tumor has been controlled, but the risk of recurrence remains high. *Neoadjuvant chemotherapy* refers to drug treatment directed at an advanced cancer to decrease preoperatively the extent or morbidity of a subsequent surgical resection. Therapy applied to recurrent disease or to a tumor that is refractory to initial treatment is termed *salvage chemotherapy.*

Table 27-1 Different Clinical Settings for Delivering Chemotherapy

Categories	Examples within Gynecologic Oncology
Induction	Metastatic gestational trophoblastic neoplasia
Adjuvant	Platinum-based chemotherapy for advanced ovarian cancer after surgical debulking
Neoadjuvant	Primary platinum-based chemotherapy for advanced ovarian cancer that is initially unresectable
Salvage	Recurrent or persistent gynecologic cancer not amenable to curative surgery or radiation

Combination Therapy

With rare exceptions, single drugs administered at clinically tolerable doses do not cure cancer. Thus, in principle, combination chemotherapy provides maximum cell kill with minimal or tolerable adverse patient side effects. Drugs are selected based on their proven efficacy as single agents, different mechanisms of action, and minimally overlapping toxicities.

Combination chemotherapy is also more likely to attack heterogeneous populations of cells with different mechanisms of resistance. Moreover, the use of multiple drugs with different mechanisms of action tends to minimize the emergence of drug resistance. Usually, drugs used in any combination should have clinical data indicating that their effects will be synergistic or at least additive. Drugs in combination should be used at their optimal doses and schedules. Dose reductions initiated solely to aid the addition of other agents is counterintuitive.

Multimodality Treatment

Frequently, chemotherapy is combined with radiation therapy or sequenced with surgery to improve patient survival. For example, the standard of care for locally advanced cervical cancer has been transformed within the past decade by adding weekly cisplatin to standard radiotherapy. As a result, patients are more likely to survive due to enhanced radiosensitivity of the tumor and/or treatment of micrometastases outside the radiation field.

However, treatment-related toxicity is also increased. Patients previously treated with radiation therapy may have bone marrow, skin, or other body systems that are more susceptible to chemotherapy toxicity. As a result, dose reductions are commonplace. Furthermore, chemotherapy is generally less effective in tumors that are within a radiated field due to increased fibrosis and destruction of microcapillaries.

Combining chemotherapy with surgery has many different applications. For example, a woman with endometrial cancer may have nodal metastases detected during surgery, and receive postoperative pelvic radiation followed by combination chemotherapy. Alternatively, a woman with recurrent ovarian cancer may be treated by combination chemotherapy with or without preceding

secondary cytoreductive surgery. The purpose of sequencing treatment in this way is to augment chemotherapy effectiveness.

Goals of Treatment

In general, chemotherapy is used with either *curative* or *palliative intent* . When implementing chemotherapy with curative intent, there are typically only a defined number of courses. For instance, after tumor debulking, a woman with advanced ovarian cancer will usually achieve remission with six cycles of platinum-based chemotherapy. Emphasis is placed on maintaining curative dosages and treatment schedule. This often leads to significant toxicity, but for the possibility of achieving cure, these side effects are typically deemed acceptable.

Chemotherapy is often not used with curative intent, and the treating clinician must balance several factors to provide effective, compassionate palliation. Chemotherapy is selected to minimize disease progression and extend quality life. Thus, in this setting, greater importance is attached to avoiding excessive toxicity. In many ways, the use of chemotherapy for palliation exemplifies the "art" of medicine. Instead of a defined number of treatment courses, a clinician must frequently re-assess the treatment effectiveness and alter chemotherapy administration accordingly.

PHARMACOLOGIC PRINCIPLES

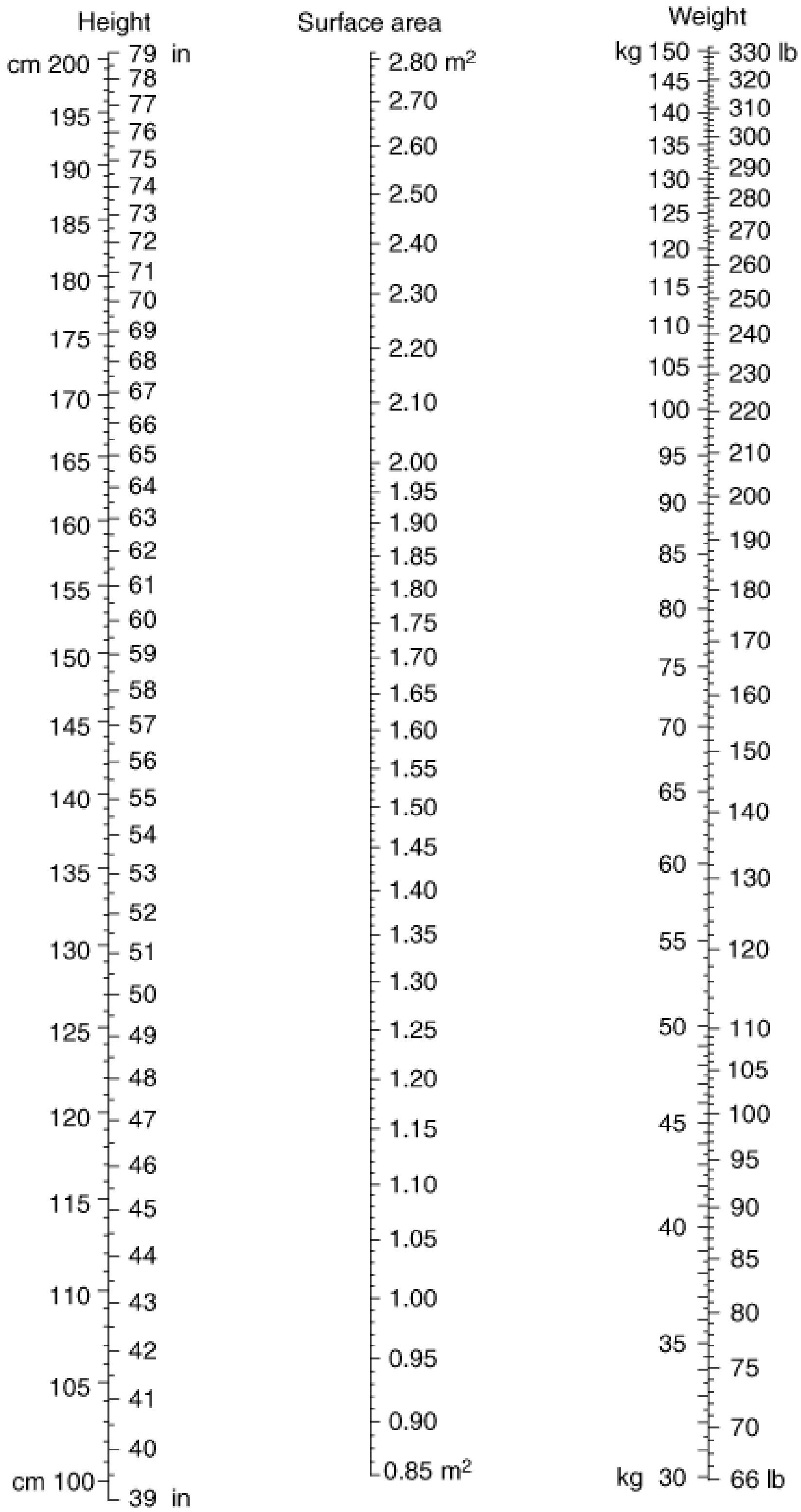
Various characteristics determine the appropriate use of chemotherapeutic drugs. Overall, treatment effectiveness depends on concentration and duration of exposure at critical tumor sites.

Drug Dosing

Chemotherapeutic agents typically have a narrow therapeutic range. Thus, doses must be calculated accurately to achieve an optimal effect and avoid undue toxicity.

Most commonly, chemotherapy dosages are calculated based on a patient's body surface area (BSA), expressed in milligrams per meter squared (mg/m^2). This modification normalizes for body frame and ensures that each patient receives proportionally similar amounts of drug. Heights and weights are obtained prior to every course of therapy. Edema or ascites must be determined, since dosages should be based on actual weight without these co-existing conditions. The BSA is most often calculated by using a nomogram (standard reference graph table) (Fig. 27-2).

FIGURE 27-2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Nomogram for calculating the body surface area (BSA) of adults. *(From DiSaia, 2002, with permission.)*

Alternatively, some drugs, such as bevacizumab, are dosed only by patient weight. In addition, carboplatin is dosed by a more complicated strategy, the Calvert formula, which includes a woman's glomerular filtration rate.

Dose Intensity

The amount of drug administered over time is known as the *dose intensity.* Its primary importance is in highly responsive tumors in which cure can be achieved with chemotherapy. However, in other less sensitive tumors, it may not be possible to increase the dose to a level sufficient to produce demonstrable benefit without producing dose-limiting toxicity. For example, trials using higher-dose chemotherapy with peripheral blood stem cell support have not improved outcomes in women with ovarian cancer. However, it is also true that reducing dose intensity to decrease toxicity can produce inferior therapeutic results.

Route of Administration

Chemotherapy may be administered systemically or regionally. Systemic therapy aims to attain maximal therapeutic cytotoxic effect without extreme toxicity to normal tissues. Oral, intravenous (IV) or intramuscular (IM) routes comprise systemic treatment options.

Regional chemotherapy is aimed at delivering drugs directly into the cavity in which the tumor is located. Clearance for many agents from a body cavity is slower than from systemic circulation. As a result, cancer cells are exposed longer to higher concentrations of active agents. This technique has been most extensively studied in ovarian cancer, in which tumors are usually confined to the intraperitoneal (IP) space. Clinical studies have uniformly demonstrated a pharmacologic advantage favoring administration into the IP compartment. However, penetration into peritoneal tumor nodules by passive diffusion is often limited by the presence of intra-abdominal adhesions, poor fluid circulation, fibrotic tumor encapsulation, and co-existing ascites. Because of these limitations in drug penetration, IP chemotherapy is typically administered to women with minimal residual disease.

During intravenous administration, several drugs are known vesicants that require special care (Table 27-2). Extravasation of these into the subcutaneous tissue can result in severe pain and necrosis. These drugs require slow infusion either through a rapidly flowing peripheral IV, or preferably via a central venous catheter. If extravasation is suspected, the infusion should be immediately stopped, the affected arm elevated, and cool packs applied. In severe cases, a plastic surgeon should be consulted.

Table 27-2 Chemotherapeutic Agents and Their Association with Extravasation Injury

Vesicants	Exfoliants	Irritants	Inflammants	Neutral
Dactinomycin	Cisplatin	Carboplatin	Methotrexate	Bleomycin
Doxorubicin	Docetaxel	Etoposide		Cyclophosphamide
Paclitaxel	Liposomal doxorubicin			Gemcitabine
Vinblastine	Topotecan			Ifosfamide
Vinorelbine				

Exfoliant, agent capable of causing skin exfoliation on extravasation; *inflammant,* agent capable of causing skin inflammation on extravasation; *irritant,* agent capable of causing skin irritation on extravasation; *vesicant,* agent capable of causing skin ulceration and tissue necrosis on extravasation.

Adapted from Mileshkin, 2004, with permission.

Excretion

Drug inactivation, elimination, or excretion dramatically influences activity and toxicity. For the most part, this takes place primarily via the liver or kidneys. As a result, drug activity may be diminished and toxicity exacerbated when there is impairment of normal liver or kidney function.

In addition, drug toxicity is often more pronounced in elderly patients or those who are malnourished. Thus, a low serum creatinine level in these women may not accurately reflect underlying renal function. If a carboplatin dose is calculated using this falsely low value, the amount may be excessive and result in considerable morbidity. Instead, a preset creatinine level may need to be selected (0.8 or 1.0 mg/dL) to aid safer dosing.

Drug Interactions

Most women who receive chemotherapy are often prescribed medication for other nonmalignant conditions, such as hypertension. Moreover, women also typically receive pain relievers, antiemetics, and antibiotics during chemotherapy. Most resultant drug interactions are probably of little consequence, but some may lead to substantially altered drug toxicity. Often drugs that are metabolized in the liver are at risk for such interactions. For example, using methotrexate in a woman taking warfarin will usually enhance the anticoagulant effect and thus requires a warfarin dose reduction.

Allergic Reaction

Despite reviewing a patient's history and administering prophylactic premedications, a woman may develop an anaphylactic, allergic, or hypersensitivity reaction during or after administration of chemotherapy. Accordingly, a treatment facility must have trained nursing staff and resources to manage these sudden but common issues.

Prior to drug administration, a woman should be informed of the necessity to report symptoms that may precede an anaphylactic reaction. Emergency equipment, such as supplemental oxygen, ventilatory face mask and bag (Ambu bag, Ambu, Glen Burnie, MD), or intubation equipment must be immediately available. For a localized hypersensitivity response, administration of diphenhydramine (Benadryl, Johnson & Johnson, New Brunswick, NJ) and/or steroids may be sufficient. However, for a generalized hypersensitivity or anaphylactic response, chemotherapy should be stopped immediately, an emergency team notified, and emergency drugs such as epinephrine (0.1 to 0.5 mg, 1:10,000 solution), administered (Table 27-3).

Table 27-3 Management of Hypersensitivity Reactions

1. Stop the chemotherapy infusion
2. Call a physician to assess the patient with regard to airway, breathing, and circulation
3. Administer intravenous normal saline if hypotensive
4. Administer oxygen if dyspneic or hypoxic
5. Administer intravenous antihistamine (e.g., 50 mg intravenous diphenhydramine or 25â€“50 mg intravenous promethazine)
6. Administer 5 mg of nebulized salbutamol if the patient has bronchospasm
7. Administer intravenous corticosteroids (e.g., 100 mg of hydrocortisone); this may have no effect on the initial reaction, but may prevent rebound or prolonged allergic manifestations
8. If the patient does not promptly improve or has symptoms of persistent or severe hypotension or persistent bronchospasm or laryngeal edema, administer adrenaline or epinephrine (0.1â€“0.25 mg intravenous); further acute resuscitation measures may be required
9. Reassure the patient that the problem is a recognized and treatable one
10. Consult a physician for a decision on further drug administration

From Mileshkin, 2004, with permission.

Drug Resistance

In principle, larger tumor masses have a greater proportion of cells that have already developed drug resistance. Resistance may be intrinsic or acquired, and it may develop to one drug or to multiple agents. In gynecologic oncology, intrinsic drug resistance is much less common. It is seen if tumors are first exposed to an agent and then fail to respond to initial treatment. In contrast, with acquired drug resistance, tumors no longer respond to drugs to which they were initially sensitive. Sometimes this occurs to a

specific drug. For instance, women with low-risk gestational trophoblastic neoplasia may become resistant to methotrexate, but remain exquisitely sensitive to dactinomycin. More often, however, acquired resistance is "pleiotropic", meaning that a cancer is resistant to multiple chemotherapy agents. Advanced ovarian cancer is a good example. Most patients will achieve remission with platinum-based chemotherapy, but 80 percent will ultimately relapse and die from tumors that have become resistant to all cytotoxic therapy.

Evaluating Response to Chemotherapy

The effective use of chemotherapy is a dynamic process whereby a treating clinician is constantly weighing toxicity to the patient against tumor response. In counseling women to continue treatment or switch to a different regimen, it is imperative to have objective criteria for response. The most important indicator is the *complete response rate* (Table 27-4). For ovarian cancer, this would include normal CA-125 levels, physical examination findings, and imaging test results. Ultimately, women who have any possibility of cure are those who first achieve a complete response. However, if chemotherapy results in a partial response, many women still view this as advantageous compared with supportive care, even if a survival benefit is unproven.

Table 27-4 Clinical End Points in Evaluating Response to Chemotherapy

End Point	Definition
Complete response	Complete resolution of all disease lasting for at least 1 month
Partial response	A decrease of ≥50 percent in the product of all measurable lesions lasting for at least 1 month without the development of new lesions
Stable disease	A decrease of <50 percent or an increase of <25 percent in the product of the diameters of all measurable disease
Progression	An increase of ≥25 percent in the measurable lesions as described above or the identification of new lesions

CHEMOTHERAPEUTIC DRUGS

In gynecologic oncology, diverse compounds that have demonstrated activity include antimetabolites, alkylating agents, antitumor antibiotics, plant alkaloids, taxanes, hormonal agents, and biologic therapies. These drugs may be used as single agents or in combination regimens.

Antimetabolites

The antimetabolites are structural and chemical analogs of naturally occurring substances in the metabolic pathways leading to the synthesis of purines, pyrimidines, and nucleic acids. In most cases, they are S phaseâ€"specific agents that are most effective in rapidly growing tumors associated with short doubling times and large growth fractions (Table 27-5).

Table 27-5 Chemotherapy Antimetabolites Used for Gynecologic Cancer					
Generic Name	**Brand Name**	**Indications**	**Routes**	**Common Dosages**	**Common Toxicity**
Methotrexate					
(MTX)	Trexall, Rheumatrex	GTN	PO, IM, IV, intrathecal	IM: 30-50 mg/m^2 IV: 100 mg/m^2 over 30 min, then 200 mg/m^2 over 12 h	BMD, mucositis, renal toxicity, CNS dysfunction
Gemcitabine	Gemzar	Recurrent ovarian CA, uterine sarcoma	IV	600-1000 mg/m^2 /wk over 30 min x 2-3 wks	BMD, N/V/D, malaise and fever

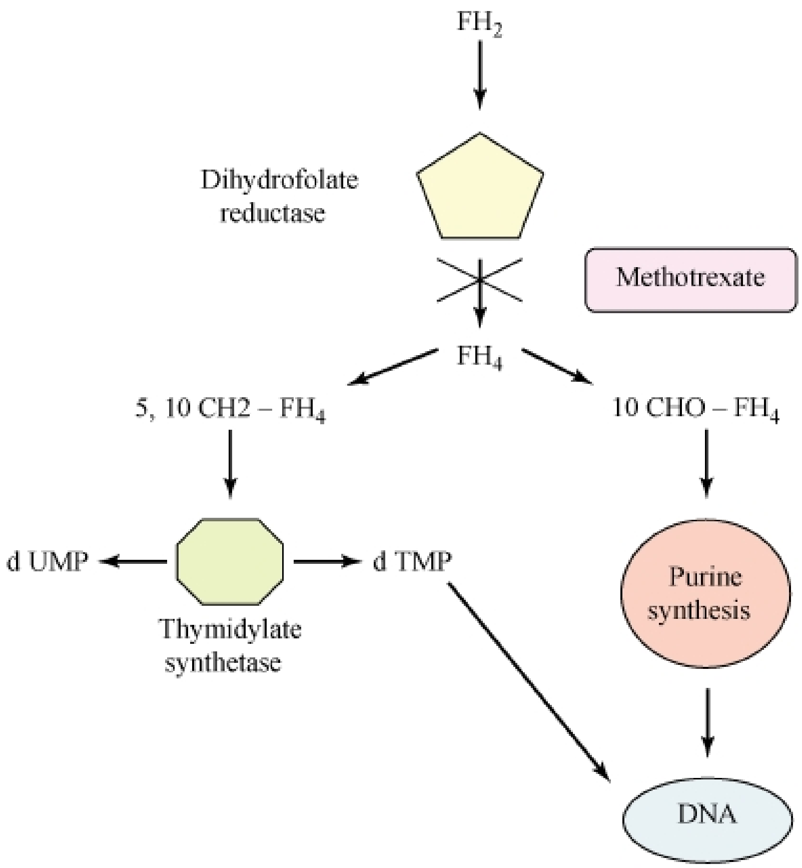
BMD = bone marrow depression; CA = cancer; CNS = central nervous system; GTN = gestational trophoblastic neoplasia; IM = intramuscular; IV = intravenous; N/A = not applicable; N/V/D = nausea, vomiting, and diarrhea; PO = orally.

METHOTREXATE

Mechanism of Action

This antimetabolite, also known as amethopterin, is most commonly used for treatment of women with gestational trophoblastic neoplasia (GTN) and ectopic pregnancy. Methotrexate (MTX) tightly binds to dihydrofolate reductase, blocking the reduction of dihydrofolate to tetrahydrofolic acid (the active form of folic acid) (Fig. 27-3). As a result, thymidylate synthetase and various steps in de novo purine synthesis are halted. This leads to arrest of DNA, RNA, and protein synthesis.

FIGURE 27-3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Methotrexate's primary target is the enzyme dihydrofolate reductase (DHFR). Inhibition of DHFR leads to partial depletion of the tetrahydrofolate cofactors, (5, 10 methylene tetrahydrofolic acid [5, 10 CH_2 -FH_4] and N-10 formyl tetrahydrofolic acid [10 CHO-FH_4]). These cofactors are required for the respective synthesis of thymidylate and purines. dTMP = deoxythymidine monophosphate; dUMP = deoxyuridine monophosphate.

Prescribing Information and Toxicity

Methotrexate may be administered orally, IM, IV, or intrathecally. Most commonly, MTX is given IM at 30 to 50 mg/m^2 weekly. Alternatively, 100 mg/m^2 IV over 30 minutes may be followed by a 200 mg/m^2 IV dose over 12 hours.

This agent causes minimal side effects at typical doses. However, at high doses, although used infrequently, MTX can lead to fatal bone marrow toxicity. This toxicity can be prevented by early administration of leucovorin (folinic acid), and this therapy is termed *leucovorin rescue.* Rescue is typically required for MTX doses over 80 mg/m^2 . With it, up to 100 mg/m^2 of leucovorin is given every 6 hours and is usually begun within 4 hours after completing MTX treatment. Further leucovorin dosing may be adjusted according to serum methotrexate levels.

In addition to myelosuppression, renal toxicity and acute cerebral dysfunction are typically only seen at high doses. Methotrexate is predominantly excreted through the kidneys, and thus women with renal insufficiency should have dosages reduced.

GEMCITABINE

Mechanism of Action

This antimetabolite is typically selected for treatment of recurrent ovarian cancer and uterine sarcomas. Gemcitabine (Gemzar, Eli Lilly, Indianapolis, IN) is a synthetic nucleoside analog that undergoes multiple phosphorylations to form the active metabolite. The resulting triphosphate is subsequently incorporated into DNA as a fraudulent base pair. Following the insertion of gemcitabine, one

additional deoxynucleotide is added to the end of the DNA chain before replication is terminated, and thereby DNA synthesis is halted.

Prescribing Information and Toxicity

The usual administration of gemcitabine is by 30-minute infusion. Durations of greater than 60 minutes are associated with dose-limiting flu-like symptoms. Depending on whether it is used as a single agent or in combination, gemcitabine is typically given between 600 to 1000 mg/m^2 once weekly for 2 to 3 weeks followed by a week of rest.

Myelosuppression, especially neutropenia, is the main dose-limiting side effect. Gastrointestinal (GI) toxicity, such as nausea, vomiting, diarrhea, or mucositis is also common. About 20 percent of patients will develop a flu-like syndrome, including fever, malaise, headache, and chills. Pulmonary toxicity is relatively uncommon, but reported.

Alkylating Agents

The alkylating agents are characterized by positively charged alkyl groups that bind to negatively charged DNA to form adducts (Table 27-6). Binding leads to DNA breaks or cross-links and a halt of DNA synthesis. In general, these drugs are cell cycleâ€"nonspecific agents that work at any phase of active replication.

Table 27-6 Chemotherapy Alkylating Agents Used for Gynecologic Cancer

Generic Name	Brand Name	Indication	Routes	Dosages	Toxicity
Cyclophosphamide	Cytoxan	GTN, recurrent ovarian CA	PO, IV	IV: 500-750 mg/m^2 over 30 min, every 3 wks	BMD, cystitis, N/V, alopecia
Ifosfamide	Ifex	Recurrent ovarian CA, cervical CA, uterine sarcoma	IV	1.2-1.6 g/m^2 /d on days 1-3 of 3-wk cycle	BMD, cystitis, N/V, alopecia, CNS and renal toxicity

BMD = bone marrow depression; CA = cancer; CNS = central nervous system; GTN = gestational trophoblastic neoplasia; IV = intravenous; N/V/D = nausea, vomiting, and diarrhea; PO = orally.

CYCLOPHOSPHAMIDE

Mechanism of Action

This alkylating agent is infrequently used, and its chief role is as part of combination chemotherapy. Cyclophosphamide is the "C" of the EMA-CO (etoposide, methotrexate, Adriamycin D, cyclophosphamide, and Oncovin [vincristine]) regimen prescribed for GTN or used as single-agent salvage therapy for recurrent epithelial ovarian cancer (Bower, 1997; Cantu, 2002). Cyclophosphamide (Cytoxan, Bristol-Myers Squibb, New York, NY) is a derivative of nitrogen mustard and is activated by a multistep process by microsomal enzymes in the liver. Its action results in DNA cross-linking and inhibition of DNA synthesis.

Prescribing Information and Toxicity

Cyclophosphamide is typically given IV at 500 to 750 mg/m^2 over 30 minutes every 3 weeks. Following administration, myelosuppression, mainly neutropenia, is the usual dose-limiting side effect. This agent is exclusively excreted by the kidneys, and hemorrhagic cystitis is a classic complication that may be delayed from 24 hours to several weeks after administration. To prevent this effect, adequate hydration is imperative to aid excretion of the metabolite acrolein, which can alkylate the bladder mucosa. In addition, GI toxicity, such as nausea, vomiting, or anorexia, is common. Alopecia is typically severe. Moreover, secondary malignancies are increased, particularly acute myelogenous leukemia and bladder cancer.

IFOSFAMIDE

Mechanism of Action

This alkylating agent is typically administered in salvage treatment of recurrent epithelial ovarian cancer, cervical cancer, and uterine sarcoma. Ifosfamide (Ifex, Bristol-Myers Squibb) is a structural analog of cyclophosphamide, differing only slightly.

However, its metabolic activation occurs more slowly than that of cyclophosphamide and leads to a greater production of chloracetaldehyde, a possible neurotoxin.

Prescribing Information and Toxicity

Ifosfamide is administered IV, usually as a short infusion. Common dosages of 1.2 to 1.6 g/m^2 are given on days 1 through 3 of a 3-week cycle. As with cyclophosphamide, adequate hydration is recommended to reduce the incidence of drug-induced hemorrhagic cystitis. In addition, the use of concurrent mesna (Mesnex, Bristol-Myers Squibb) is required to prevent severe hematuria. A metabolite of mesna chemically binds with the urotoxic ifosfamide metabolite, acrolein, and detoxifies it.

Overall, side effects are similar to those of cyclophosphamide. However, neurotoxicity, manifested as lethargy, confusion, seizure, ataxia, hallucinations, and occasionally coma, are more likely. These symptoms are caused by the chloracetaldehyde metabolite and are spontaneously reversible.

Antitumor Antibiotics

The antitumor antibiotics are generally derived from microorganisms. Most antitumor antibiotics exert their cytotoxic effects by DNA intercalation, and as a group, they are cell-cycle nonspecific.

DACTINOMYCIN

Mechanism of Action

This agent is used to treat GTN as a single agent or as part of combination chemotherapy (Table 27-7). Dactinomycin (Cosmegen, Merck & Co., Whitehouse Station, NJ), also known as Adriamycin D, is the "A" of the EMA-CO chemotherapy combination. Dactinomycin is a product of the genus *Streptomyces* and becomes anchored into purine-pyrimidine DNA base pairs, resulting in inhibition of DNA synthesis. Toxic oxygen-free radicals also cause DNA breaks. Dactinomycin is mainly excreted through the biliary system.

Table 27-7 Chemotherapeutic Antibiotics Used for Gynecologic Cancer

Generic Name	Brand Name	Indication	Route	Dosage	Toxicity
Actinomycin D (dactinomycin)	Cosmegen	GTN	IV	1.25 mg IV push every other wk or 0.5 mg on days 1-5, every 2-3 wks	BMD, N/V/D, alopecia, vesicant
Bleomycin	Blenoxane	Germ cell or SCST ovarian CA, GTN	IV, IM, SC, intrapleurally	IV: 20 U/m^2 (maximum dose of 30 U), every 3 wks	Pulmonary toxicity, fever, skin reaction
Doxorubicin	Adriamycin	Endometrial CA, recurrent epithelial ovarian CA	IV	45-60 mg/m^2 every 3 wks	BMD, cardiac toxicity, alopecia, vesicant
Liposomal doxorubicin	Doxil	Recurrent epithelial ovarian CA	IV	40-50 mg/m^2 over 30 min, every 4 wks	PPE, stomatitis, infusion reaction

BMD = bone marrow depression; CA = cancer; GTN = gestational trophoblastic neoplasia; IM = intramuscular; IV = intravenous; N/V/D = nausea, vomiting, and diarrhea; PPE = palmar-plantar erythrodysesthesia; SC = subcutaneous; SCST = sex cord-stromal tumor.

Prescribing Information and Toxicity

The usual "pulse" dose of dactinomycin is 1.25 mg IV push every other week or 0.5 mg on days 1 through 5 every 2 to 3 weeks. Myelosuppression is the main dose-limiting side effect and it may be severe. Moreover, GI toxicity, including nausea, vomiting, mucositis, and diarrhea are often significant. Alopecia is common. As with others in the antibiotic group, dactinomycin is a potent

vesicant that can cause skin ulceration and tissue necrosis if extravasated during IV infusion (Route of Administration).

BLEOMYCIN

Mechanism of Action

This antitumor antibiotic is the "B" in BEP (bleomycin, etoposide, and cisplatin) regimens, which are used as adjuvant treatment of malignant ovarian germ cell or sex cord-stromal tumors (Homesley, 1999; Williams, 1991). Additionally, it is used in salvage treatment of GTN (DuBeshter, 1989).

Bleomycin (Blenoxane, Bristol-Myers Squibb), when complexed with iron, creates activated oxygen-free radicals, which cause DNA strand breaks and cell death. It is cell-cycle specific and maximally effective during the G_2 phase.

Prescribing Information and Toxicity

The usual dose of bleomycin is 20 U/m^2 IV (maximum dose of 30 units), given every 3 weeks. The dosage is quantitated in international units of cytotoxic activity. Bleomycin can also be administered by the IM, subcutaneous (SC), or intrapleural routes.

Pulmonary toxicity is the main dose-limiting side effect, developing in 10 percent of patients. Accordingly, for women prescribed bleomycin, chest radiographs and clinical auscultation should be performed regularly. Typically, pneumonitis with cough, dyspnea, dry inspiratory crackles, and infiltrates on chest radiograph result. This complication is more common in patients older than 70 years and with cumulative doses of greater than 400 units. Pulmonary function tests (PFTs) with special focus on carbon monoxide diffusion in the lung (DL_{CO}) and vital capacity should be obtained at baseline and during therapy. A 15-percent decrease in pulmonary function requires discontinuation of bleomycin. In addition to pulmonary effects, skin reactions with bleomycin are common, but this drug is not myelosuppressive.

DOXORUBICIN

Mechanism of Action

This antitumor antibiotic is the "A" in the combination chemotherapy TAP (taxol, Adriamycin, and cisplatin), used for endometrial cancer. Doxorubicin (Adriamycin, Pfizer, New York, NY) is also used for recurrent epithelial ovarian cancer.

This agent intercalates into DNA to inhibit DNA synthesis, inhibits topoisomerase II, and forms cytotoxic oxygen-free radicals. The drug is metabolized extensively in the liver and eliminated through biliary excretion.

Prescribing Information and Toxicity

The usual dose of doxorubicin is 45 to 60 mg/m^2 IV as part of combination chemotherapy, repeated every 3 weeks. Myelosuppression, particularly neutropenia, is the main dose-limiting side effect. However, cardiotoxicity is a classic complication. Patients should be monitored with a multiple gated acquisition (MUGA) radionuclide scan at baseline and periodically during therapy. The risk of cardiotoxicity is higher in women older than 70 years and those with cumulative doses exceeding 550 mg/m^2 . Ultimately, women may develop a dilated cardiomyopathy associated with congestive heart failure. Gastrointestinal toxicities are generally mild, but alopecia is universal.

LIPOSOMAL DOXORUBICIN

Mechanism of Action

This antitumor antibiotic is used in salvage treatment of recurrent epithelial ovarian cancer (Gordon, 2004). The liposomal encapsulation of doxorubicin (Doxil, Ortho Biotech, Bridgewater, NJ) dramatically alters the pharmacokinetic and toxicity profiles of the drug. Researchers developed liposomal doxorubicin to reduce cardiotoxicity and to selectively target the drug to tumor tissues.

Prescribing Information and Toxicity

Liposomal doxorubicin may be administered as an IV infusion over 30 to 60 minutes and is dosed at 40 to 50 mg/m^2 every 4 weeks. Administration is associated with minimal nausea, vomiting, alopecia, and cardiotoxicity. Infusion-related reactions develop in less than 10 percent of patients and are most common during the first course of treatment. However, an increased rate of stomatitis and palmar-plantar erythrodysesthesia (PPE) is noted. At first, PPE causes redness and dysesthesias of the palms and

soles. Initial tingling sensations may advance to discomfort, and distal extremity swelling may be noted. As toxicity progresses, ulceration within extremity skin creases and desquamation may follow.

Plant-Derived Agents

A common theme in the cytotoxic activity of these agents is disturbance of normal assembly, disassembly, and stabilization of intracellular microtubules. The group includes the taxanes, vinca alkaloids, and topoisomerase inhibitors.

TAXANES

Paclitaxel and docetaxel are both cell cycleâ€"specific agents that have maximal activity during the M phase (Table 27-8). They act to "poison" the mitotic spindle by preventing depolymerization of the microtubules and inhibiting cellular replication. Paclitaxel is derived from the needles and bark of the western yew, *Taxus brevifolia.* Docetaxel is a semi-synthetic analog of paclitaxel derived from the European yew tree.

Table 27-8 Chemotherapeutic Plant Alkaloids Used for Gynecologic Cancer

Generic Name	Brand Name	Indications	Routes	Dosages	Toxicity
Paclitaxel	Taxol	Recurrent epithelial ovarian CA, endometrial CA, cervical CA, GTN	IV	135-175 mg/m^2 every 3 wks	HSR, peripheral neurotoxicity, BMD, alopecia, bradycardia and arrhythmia
Docetaxel	Taxotere	Recurrent epithelial ovarian CA, uterine sarcoma	IV	75-100 mg/m^2 every 3 wks	BMD, peripheral edema, HSR, alopecia
Vincristine	Oncovin	GTN	IV	0.8-1.0 mg/m^2 every other wk	Neurotoxicity, abdominal pain, alopecia
Vinblastine	Velban	GTN	IV	9 mg/m^2 every 3 wks	BMD, N/V/D, mucositis, HTN, neurotoxicity, alopecia
Vinorelbine	Navelbine	Recurrent epithelial ovarian CA, cervical CA	IV	30 mg/m^2 every wk	BMD, N/V/D, stomatitis, peripheral neurotoxicity
Etoposide	VP-16	Germ cell or SCST ovarian CA; recurrent epithelial ovarian CA; endometrial CA	IV, PO	IV: 75 mg/m^2 , days 1-5, every 3 wks	BMD, alopecia, secondary cancers
Topotecan	Hycamtin	Recurrent epithelial ovarian CA, cervical CA	IV	1.5 mg/kg/d, days 1-5, every 3 wks	BMD, N/V, alopecia, fever, malaise

BMD = bone marrow depression; CA = cancer; GTN = gestational trophoblastic neoplasia; HSR = hypersensitivity reaction; HTN = hypertension; IV = intravenous; N/V/D = nausea, vomiting, and diarrhea; PO = orally; SCST = sex cord-stromal tumor.

Paclitaxel

One of the most widely used agents, paclitaxel (Taxol, Bristol-Myers Squibb) is used for treatment of primary or recurrent epithelial ovarian, endometrial, and cervical cancers, and GTN.

Prescribing Information and Toxicity

Paclitaxel's usual dose is 135 to 175 mg/m^2 given IV over 3 hours, every 3 weeks. For recurrent ovarian cancer, weekly paclitaxel is also effective at 80 mg/m^2 IV for 3 consecutive weeks on a 28-day schedule (Markman, 2006).

Myelosuppression is the usual dose-limiting side effect. In addition, a hypersensitivity reaction occurs in about one third of patients due to its formulation in Cremophor-EL (BASF, Florham Park, NJ), an emulsifying agent. Typically, the reaction develops within

minutes of starting an initial infusion. Fortunately, the incidence can be decreased 10-fold by premedication with steroids, usually dexamethasone, 20 mg orally 12 and 6 hours before administration. Neurotoxicity is the principal nonhematologic dose-limiting side effect. Common symptoms include numbness, tingling, and/or burning pain in a stocking-glove distribution. Peripheral neuropathy progresses with increased paclitaxel exposure and may become debilitating. Alopecia is almost universal and results in total loss of body hair.

Docetaxel

This taxane may be used to treat recurrent epithelial ovarian cancer and uterine sarcoma (Bay, 2006; Strauss, 2007). In addition, patients with worsening neurotoxicity with paclitaxel are often switched to docetaxel since clinical efficacy is thought to be similar.

Prescribing Information and Toxicity

The usual dose of docetaxel (Taxotere, Sanofi-Aventis, Bridgewater, NJ) is 75 to 100 mg/m^2 IV, repeated every 3 weeks. For recurrent ovarian cancer, weekly docetaxel is also effective at 35 mg/m^2 IV for 3 consecutive weeks on a 28-day schedule (Tinker, 2007).

Myelosuppression is the main dose-limiting side effect. Fluid retention syndrome occurs in about half of patients, manifesting as weight gain, peripheral edema, pleural effusion, and ascites. Steroid prophylaxis prevents most of this toxicity, as well as dermatologic side effects and hypersensitivity reactions.

VINCA ALKALOIDS

Vincristine, vinblastine, and vinorelbine are cell cycleâ€"specific drugs derived from the periwinkle plant with maximal activity in the M phase. These compounds inhibit normal microtubular polymerization by binding to the tubulin subunit at a site distinct from the taxane-binding site.

Vincristine

This vinca alkaloid represents the "O" of EMA-CO combination chemotherapy for GTN treatment. The usual dose of vincristine (Oncovin, Eli Lilly) is 0.8 to 1.0 mg/m^2 , given IV every other week. To prevent or delay the development of neurotoxicity, the total individual dose should be capped at 2 mg.

Neurotoxicity is the most common dose-limiting toxicity, and may include peripheral neuropathy, autonomic nervous system dysfunction, cranial nerve palsies, ataxia, or seizures. Moreover, concurrent administration with other neurotoxic agents such as cisplatin and paclitaxel may increase severity. Gastrointestinal toxicity is also common, including constipation, abdominal pain, and paralytic ileus. However, myelosuppression is typically mild.

Vinblastine

This vinca alkaloid may be used in salvage treatment for GTN. The usual dose of vinblastine (Velban, Eli Lilly) varies, but one approach administers 9 mg/m^2 IV every 3 weeks. This agent is toxic and as a result, not commonly used. Myelosuppression is the main dose-limiting side effect. Gastrointestinal toxicity may be severe and includes mucositis, stomatitis, nausea, vomiting, anorexia, and diarrhea or constipation. In addition, hypertension may result from autonomic dysfunction. Neurotoxicity develops much less frequently, but is similar to that seen with vincristine.

Vinorelbine

This vinca alkaloid is a semisynthetic derivation of vinblastine and is used in salvage treatment for recurrent epithelial ovarian cancer and for treatment of cervical cancer. The usual dose of vinorelbine (Navelbine, GlaxoSmithKline, Philadelphia, PA) is 30 mg/m^2 given IV, as a single agent or in combination. It is given on a weekly basis, with a week off in a 21- or 28-day schedule.

Myelosuppression is the main dose-limiting side effect. Moreover, GI toxicity is common and has symptoms similar to those of vinblastine. Neurotoxicity is usually mild, particularly compared with other vinca alkaloids.

TOPOISOMERASE INHIBITORS

The topoisomerase (TOPO) inhibitors are semisynthetic cytotoxic agents derived from the mandrake plant. This group of agents

may be further divided into categories based on the TOPO enzyme they inhibit. The podophyllotoxins are those that inhibit TOPO II and include etoposide. The camptothecins inhibit TOPO I and include topotecan.

ETOPOSIDE

Mechanism of Action

This agent is often used intravenously as part of combination chemotherapy. Etoposide represents the "E" of the EMA-CO regimen, which is used for GTN. In addition, it is a component of the BEP regimen, used for ovarian germ cell or sex cord-stromal tumors. Oral etoposide may be efficacious as a single agent for salvage treatment of recurrent epithelial ovarian cancer or endometrial cancer.

Etoposide (VP-16, Bristol-Myers Squibb) is a cell cycleâ€"specific agent with maximal activity in the late S and G_2 phase. This drug "poisons" the TOPO II enzyme by stabilizing an otherwise transient form of the TOPO II-DNA complex. As a result, DNA cannot unwind.

Prescribing Information and Toxicity

The usual dose of etoposide varies. In the EMA-CO regimen, 100 mg/m^2 is administered IV on days 1 and 2, every 2 weeks. In the BEP regimen, it is usually prescribed as 75 mg/m^2 IV on days 1 through 5, and given every 3 weeks. The oral dose is 50 mg/m^2 /d for a 21-day course, followed by a week off on a 28-day schedule. Up to 95 percent of etoposide is protein-bound, mainly to albumin. Thus, decreased albumin levels result in a higher fraction of free drug and potentially a higher incidence of toxicity.

Myelosuppression, most commonly neutropenia, is the main dose-limiting side effect with etoposide. Gastrointestinal symptoms of nausea, vomiting, and anorexia are usually minor, except with oral administration. Most patients will develop alopecia. With etoposide, there is an increased risk of secondary malignancies, especially acute myelogenous leukemia, particularly if the total dose exceeds 2,000 mg/m^2 .

TOPOTECAN

Mechanism of Action

This agent is a semisynthetic analog of the alkaloid extract camptothecin and inhibits TOPO I function. It binds to and stabilizes a transient TOPO I-DNA complex, resulting in double-strand breakage and lethal DNA damage. Topotecan (Hycamtin, GlaxoSmithKline) is used in salvage therapy of recurrent epithelial ovarian cancer and recurrent cervical cancer (Long, 2005).

Prescribing Information and Toxicity

Topotecan is administered IV, by two different schedules. The standard dosage for recurrent ovarian cancer is 1.5 mg/m^2 for days 1 through 5, given every 3 weeks (Gordon, 2004). However, this schedule is associated with a greater than 80-percent incidence of severe neutropenia. A less toxic regimen is 4 mg/m^2 weekly for 3 weeks during a 28-day schedule (Spannuth, 2007). The usual dose when combined with cisplatin for recurrent cervical cancer is 0.75 mg/m^2 on days 1 through 3, given every 3 weeks (Long, 2005).

Myelosuppression, most commonly neutropenia, is the main dose-limiting side effect. Gastrointestinal toxicity is also common, and includes nausea, vomiting, diarrhea, and abdominal pain. Systemic symptoms such as headache, fever, malaise, arthralgias, and myalgias are typical. Alopecia is often as complete as that seen with paclitaxel therapy.

Miscellaneous

Several antineoplastic compounds do not clearly fit into any of the above categories. In general, these cell cycleâ€"nonspecific drugs have similarities to alkylating agents.

CARBOPLATIN

Mechanism of Action

This agent is one of the most widely used, particularly in adjuvant or salvage treatment of epithelial ovarian and endometrial cancers. Carboplatin (Paraplatin, Bristol-Myers Squibb) produces DNA adducts that inhibit DNA synthesis.

Prescribing Information and Toxicity

The usual IV dose of carboplatin is calculated to a target area under the curve (AUC) of 6, based on the glomerular filtration rate (GFR). For dose calculation, the Calvert equation is the most frequently used [carboplatin total dose (mg) = AUC x (GFR + 25)]. In clinical practice, the estimated creatinine clearance (CrCl) is usually substituted for the GFR and may be calculated by the Cockcroft-Gault equation [CrCl = (140 â€“ age) x weight (kg)/0.72 x serum creatinine level (mg/100 mL)]. The infusion takes about 30 minutes and dosing is repeated every 3 weeks.

Myelosuppression, most commonly thrombocytopenia, is the main dose-limiting side effect. Gastrointestinal toxicity and peripheral neuropathy are notably less compared with cisplatin. Hypersensitivity reactions will eventually develop in up to 25 percent of women receiving more than six cycles.

CISPLATIN

Mechanism of Action

Similar to carboplatin, this agent produces DNA adducts that inhibit DNA synthesis (see Fig. 28-11). Cisplatin (CDDP, Bristol-Myers Squibb) is one of the most widely used agents. It may be given concomitantly with radiation as a radiosensitizing agent for primary treatment of cervical cancer, or either as a single agent or in combination for recurrent cervical cancer. For ovarian germ cell or sex cord-stromal tumors, cisplatin is part of combination chemotherapy as the "P" of BEP. It is also a member of combination chemotherapy as the "P" of TAP for advanced or recurrent endometrial cancer. However, for use in epithelial ovarian cancer, cisplatin has largely been replaced by carboplatin, except for IP therapy.

Prescribing Information and Toxicity

The usual dose of cisplatin varies, depending on the indication. In cervical cancer, it is given at 40 mg/m^2 IV weekly during radiation therapy, or 50 mg/m^2 IV every 3 weeks for patients with recurrent disease (Long, 2005). The 50-mg/m^2 dose is also used in the TAP regimen every 3 weeks (Fleming, 2004). As part of the BEP protocol, cisplatin is administered 20 mg/m^2 IV on days 1 through 5 every 3 weeks. Alternatively, for ovarian cancer IP chemotherapy, it is given on day 2 of a 21-day cycle at a dosage of 75 to 100 mg/m^2 (Armstrong, 2006).

Cisplatin has several significant adverse effects associated with administration. Of these, nephrotoxicity is the main dose-limiting side effect. Accordingly, patients must be aggressively hydrated before, during, and after drug administration. Mannitol (10 g) or furosemide (20 to 40 mg) may be necessary to maintain a urine output of at least 100 to 150 mL/h. With cisplatin administration, electrolyte abnormalities, such as hypomagnesemia and hypokalemia, are common. In addition, severe, prolonged nausea and vomiting can be dramatic without adequate premedication (Table 27-9). Patients often describe a metallic taste and loss of appetite following treatment. Neurotoxicity, usually in the form of peripheral neuropathy, can also be dose limiting and irreversible. Ototoxicity typically manifests as high-frequency hearing loss and tinnitus. Similarly to carboplatin, hypersensitivity reactions may develop, and overall cisplatin is significantly more toxic than carboplatin.

Table 27-9 Dose and Schedule of Antiemetics to Prevent Emesis Induced by Antineoplastic Therapy of High Emetic Risk			
Antiemetics for Intravenous Antineoplastic Therapy of Moderate Emetic Risk	**Brand Name**	**Single Dose Administered Before Chemotherapy**	**Single Dose Administered Daily**
5-HT_3 serotonin receptor antagonists			
Granisetron	Kytril	Oral: 2 mg IV: 1 mg or 0.01 mg/kg	
Ondansetron	Zofran	Oral: 24 mg IV: 8 mg or 0.15 mg/kg	
Palonosetron	Aloxi	IV: 0.25 mg	
Dexamethasone	Decadron	Oral: 12 mg	Oral: 8 mg, days 2-4
Aprepitant	Emend	Oral: 125 mg	Oral: 80 mg, days 2 and 3

5-HT_3 = 5-hydroxytryptamine-3; IV = intravenous.

Adapted from Kris, 2006, with permission.

HEXAMETHYLMELAMINE

This agent forms DNA cross-links, but its exact chemotherapeutic mechanism of action is unknown. Hexamethylmelamine, also called altretamine (Hexalen, MGI Pharma, Bloomington, MN), is used in consolidation therapy of advanced epithelial ovarian cancer and in salvage treatment of recurrent epithelial ovarian cancer (Alberts, 2004; Rustin, 1997).

The usual dose of hexamethylmelamine is 260 mg/m^2 daily, given as four divided oral doses for 14 to 21 consecutive days in a 28-day cycle. Gastrointestinal side effects, such as nausea and vomiting, are the usual dose-limiting toxicity. Myelosuppression is also common. In addition, approximately one quarter of patients will develop neurotoxicity, manifested as lethargy, agitation, or peripheral neuropathy.

Hormonal Agents

Due to their minimal toxicity and reasonable activity, hormonal agents are commonly used for the treatment of endometrial, ovarian, and breast cancers.

TAMOXIFEN

This drug is a nonsteroidal anti-estrogen that competes for binding to the estrogen receptor. The complex is then transported to the tumor cell nucleus, where it binds to DNA and inhibits cellular growth and proliferation. As such, tamoxifen (Nolvadex, AstraZeneca, Wilmington, DE) is indicated in the treatment of endometrial cancer and recurrent epithelial ovarian cancer (Fiorica, 2004; Markman, 2004). It is usually prescribed in dosages of 20 to 40 mg orally daily. The toxicity associated with tamoxifen in minimal, but menopausal symptoms are common. Moreover, fluid retention and peripheral edema develop in one third of patients.

MEGESTROL ACETATE

This agent is a synthetic derivative of progesterone that has activity on tumors through its anti-estrogenic effects. As such, megestrol acetate (Megace, Bristol-Myers Squibb) is used to treat recurrent endometrial cancer, and the usual dosage is 40 mg orally, four times daily.

This drug has minimal toxicity. However commonly patients gain weight from a combination of fluid retention and increased

appetite.

BIOLOGICAL THERAPY

Although this field is still in its infancy, biological therapy is designed to more accurately target specific tumors while avoiding much of the toxicity seen in conventional chemotherapy. This approach is often referred to as *immunotherapy* or *biological response modifier therapy.* Such novel therapeutic designs may enhance the chemosensitivity of malignant cells to treatment or may use the body's own immune system to attack the cancer. Many new treatments are currently being tested. Ultimately, the long-term goal is to improve cancer patient outcome, especially in those with tumors that are resistant to standard therapy.

Bevacizumab

This agent is a monoclonal antibody that works as an anti-angiogenic agent. Currently, the use of bevacizumab (Avastin, Genentech, South San Francisco, CA) is investigational and indicated primarily in heavily pretreated recurrent epithelial ovarian cancer (Wright, 2006). Its usual dose is 15 mg/kg IV, given every 3 weeks with or without cytotoxic chemotherapy. In most cases, the toxicity with bevacizumab is minimal. However, GI perforation occurs in up to 10 percent of patients. Elevated blood pressure is common and may lead to hypertensive crisis. Other possible toxicities include incomplete wound healing, weakness, pain, nosebleed, or proteinuria.

Oregovamab

This monoclonal antibody was designed to bind with high affinity to CA125, and thereby help the immune system recognize and attack ovarian cancers. Oregovamab (OvaRex, Unither Pharamaceuticals, Wellesley Hills, MA) is currently under investigation for the treatment of epithelial ovarian cancer. Its usual dose is 2 mg IV, given as a short infusion, several times per year. This therapy has minimal toxicity, but pain, myalgia, arthralgia, and diarrhea have been reported (Berek, 2004).

VACCINES

Therapeutic cancer vaccines are designed to induce cellular components of the immune system to recognize and attack tumors. Malignant cells that express specific surface antigens can thereby be targeted and destroyed. For example, in cervical cancer, viral peptides derived from human papillomavirus (HPV) E6 and E7 oncoproteins have been clinically tested (Borysiewicz, 1996). Additionally, ovarian cancer patients have been studied with a vaccine directed at CA125 (Reinartz, 2004).

For the most part, such strategies have not been clinically effective due to a number of obstacles. Only a limited number of shared tumor-associated antigens have been identified; epitopes for cellular immunity have not been adequately defined; and few tumor antigens are unique. Tumors commonly lose their distinctive antigen expression and may undergo mutation. In general, vaccine trials are performed with patients with advanced disease. However, in these situations clinical response is difficult to evaluate and statistically uninformative. In addition, inherent systemic immunosuppression in women with advanced disease may prevent an adequate immune response.

In contrast, prophylactic vaccines, such as the recent emergence of the HPV vaccine, have shown great promise for preventing cervical cancer (Harper, 2004; Villa, 2005). These vaccines work by eliciting humoral immune responses to induce the production of antibodies capable of neutralizing a virus before infection (see Chap. 29, Prophylactic Vaccines).

SIDE EFFECTS

Chemotherapy regimens are universally toxic and display a narrow margin of safety. Several agents are associated with classic toxicities that can often be anticipated, and thereby avoided. Because of their limited therapeutic ranges, most agents require dosage adjustment in accordance with individual patient tolerances. Initial chemotherapy dosing is calculated from BSA, weight, renal function, and hepatic function, using specified guidelines from clinical trials. However, numerous other factors influence toxicity and include the patient's baseline nutrition, overall health, extent of disease, and prior therapy. The Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI) has developed a detailed and comprehensive set of guidelines for the description and grading of toxicity in collaboration with the Food and Drug Administration (FDA), national cooperative groups, and the pharmaceutical industry (current version: http://ctep.info.nih.gov).

In general, treatment modifications depend on the degree (grade) and duration of toxicity experienced during the preceding therapy course. Doses should be reduced if a woman experiences a severe reaction, but then may be subsequently increased if tolerance improves. However, treatment should not resume until toxicity has resolved to baseline or "grade 1" levels and may be delayed on a week-to-week basis to allow for recovery. Dose modification and supportive care should be implemented to prevent delays of greater than 2 weeks, which would otherwise compromise the therapy efficacy. Serious myelosuppression can be partially corrected with the use of hematopoietic growth factors (Growth Factors). Many of the common toxicities can be prevented with proper use of premedications or alleviated with supportive measures.

Bone Marrow Toxicity

Myelosuppression, especially neutropenia, is the most common dose-limiting side effect of cytotoxic drugs. The absolute neutrophil count (ANC) is most important when determining the risk of infection. The ANC may reflect mild (1,000 to 1,500/mm^3), moderate (500 to 1,000/mm^3) or severe (<500/mm^3) neutropenia. In addition, moderate degrees of anemia are common in cancer patients receiving chemotherapy, which may contribute to chronic fatigue. Frequent transfusions are not practical or recommended, and many patients will adapt to chronic anemia with minimal symptoms. Thrombocytopenia is less common, but may predispose the patient to serious bleeding if a platelet count is <10,000/mm^3 .

Gastrointestinal Toxicity

Most anticancer agents are associated with some degree of nausea, vomiting, and anorexia. Typically, the emetogenic potential of a particular drug or regimen will dictate the anti-emetic regimen used (Tables 27-10 and 27-11). Mild nausea and vomiting can often be managed effectively by prochlorperazine with or without dexamethasone (see Table 39-13). For drugs with more severe emetogenic effects such as cisplatin, the 5-hydroxytryptamine antagonists can be given IV before chemotherapy. The group includes ondansetron, granisetron, and palonosetron. Ondansetron and granisetron may also be provided orally to manage delayed and/or chronic nausea after chemotherapy. Diarrhea, oral mucositis, esophagitis, and gastroenteritis are treated with supportive care.

Table 27-10 Emetic Risk of Intravenously Administered Antineoplastic Agents

Emetic Risk (incidence of emesis without antiemetics)	**Agent**
High (>90%)	Cisplatin Cyclophosphamide ≧ 1,500 mg/m^2 Dactinomycin
Moderate (30â€“90%)	Carboplatin Ifosfamide Cyclophosphamide <1,500 mg/m^2 Doxorubicin
Low (10â€“30%)	Paclitaxel Docetaxel Topotecan Etoposide Methotrexate Gemcitabine
Minimal (<10%)	Bevacizumab Bleomycin

	Vinblastine Vincristine Vinorelbine

Adapted from Kris, 2006, with permission.

Table 27-11 Drug Regimens for the Prevention of Chemotherapy-Induced Emesis by Emetic Risk Category	
Emetic Risk Category (incidence of emesis without antiemetics)	**Antiemetic Regimens and Schedules**
High (>90%)	5-HT_3 serotonin receptor antagonist: day 1 Dexamethasone: days 1â€“3 Granisetron: days 1â€“3
Moderate (30% to 90%)	5-HT_3 serotonin receptor antagonist: day 1 Dexamethasone: days 1â€“3
Low (10% to 30%)	5-HT_3 serotonin receptor antagonist: day 1 Dexamethasone: days 1â€“3
Minimal (<10%)	Prescribe as needed

5-HT_3 = 5-hydroxytryptamine-3.

Modified from Kris, 2006, with permission.

Dermatologic Toxicity

Most drugs can cause a spectrum of toxicity to the skin or subcutaneous tissues, including hyperpigmentation, photosensitivity, nail abnormalities, rashes, urticaria, or erythema. Many of these are drug-specific and self-limited, but occasionally they may be dose-limiting. As discussed earlier, PPE is a known toxicity of liposomal doxorubicin (Prescribing Information and Toxicity). In addition, changes in skin pigmentation are seen with bleomycin, whereas nail discoloration and oncholysis have been associated with docetaxel therapy. Premedication with diphenhydramine hydrochloride will prevent or alleviate mild urticarial reactions.

Neurotoxicity

Peripheral neuropathy occurs commonly with cisplatin, paclitaxel, vinca alkaloids, and hexamethylmelamine. Cisplatin-induced neurotoxicity usually resolves slowly, due to axonal demyelination and loss. This toxicity is related to cumulative dose and intensity, and to counter this toxicity, amifostine (Ethyol, MedImmune, Gaithersburg, MD) may be administered. Amifostine is a prodrug that is dephosphorylated by alkaline phosphatase in tissues to a pharmacologically active free thiol metabolite. This metabolite is believed to reduce cisplatin cumulative toxicity. Although amifostine has been reported to reduce the frequency and severity of platinum-mediated neuropathy, substitution of carboplatin will avoid much of the toxicity.

With chemotherapeutic agents in general, drug dosing may need to be adjusted if peripheral neuropathy becomes problematic, for example, if a patient can no longer hold a cup of coffee. More dramatic instances of acute cerebellar syndromes, cranial nerve palsies or paralysis, and occasionally acute and chronic encephalopathies should be managed with supportive care, and usually discontinuation of the offending agent.

Alopecia

One of the most emotionally distressing side effects of many chemotherapeutic agents is scalp alopecia. Fortunately, this is usually

reversible. With some drugs such as paclitaxel, women will also experience loss of eyelashes, eyebrows, and other body hair. In general, techniques to minimize alopecia are unsuccessful. Instead, women should be counseled regarding cosmetic options such as false eyelashes and wigs.

GROWTH FACTORS

The routine incorporation of hematopoietic drug factors into the administration of chemotherapy produces dramatic results. These commonly used agents are usually given by subcutaneous injection. Of these, epoetin alfa and darbepoetin alfa stimulate red blood cell (RBC) production, prevent the need for frequent blood transfusion, and combat therapy-related fatigue. Alternatively, filgrastim and pegfilgrastim increase granulocyte production, and thereby allow women to continue their treatment schedule without dose delays due to moderate or severe neutropenia.

Epoetin Alfa

This hematopoietic drug is a recombinant glycoprotein that has the same biologic effects as endogenous erythropoietin. As such, it stimulates division and differentiation of RBCs within the bone marrow and is indicated in the treatment of chemotherapy-induced anemia. Epoetin alfa (Procrit, Ortho Biotech, Raritan, NJ, and Epogen, Amgen, Thousand Oaks, CA) is usually prescribed as 40,000 units SC, given weekly (Case, 2006). Beyond local pain at the injection site, this agent has minimal side effects. Possible toxicity may include diarrhea, nausea, or hypertension.

Darbepoetin Alfa

This hematopoietic drug is closely related to epoetin alfa and has the same biologic effects as endogenous erythropoietin. Indicated for the treatment of chemotherapy-induced anemia, the usual SC dose of darbepoetin alfa (Aranesp, Amgen) is 200 μg every other week or 500 μg given every 3 weeks. Darbepoetin alfa has minimal side effects beyond local pain at the injection site. However, use should be discontinued if hemoglobin levels exceed 12 mg/dL to avoid thromboembolic events or other cardiovascular morbidity.

Filgrastim

This protein is a human granulocyte colony-stimulating factor (G-CSF), produced by recombinant DNA technology. As such, filgrastim (Neupogen, Amgen) is a pleiotropic cytokine that binds to hematopoietic cells and activates the proliferation, differentiation, and activation of granulocyte progenitor cells. This agent is indicated as an adjunct to chemotherapy. It allows women to continue their chemotherapy schedule without dose delays from myelosuppression and/or speeds resolution of neutropenic fever episodes.

The usual SC dose of filgrastim is 5 μg/kg/d, but typically patients are given either 300 μg or 480 μg, which is the content of manufactured vials. It must be administered at least 24 hours after the completion of chemotherapy. Therapy should be terminated if white blood counts exceed 10,000/mm^3 or if absolute neutrophil counts exceed 1,000/mm^3 for 3 consecutive days. Toxicity with filgrastim is limited, and transient bone pain is usually mild to moderate.

Pegfilgrastim

This agent acts similarly to filgrastim to stimulate production of granulocyte progenitor cells within the bone marrow. The "peg" in pegfilgrastim (Neulasta, Amgen) refers to a polyethylene glycol unit that prolongs the length of time it remains in the body. Pegfilgrastim is given as a single 6-mg SC injection once per chemotherapy cycle. This is usually far more convenient than daily doses. It should not be administered during the period 14 days before and 24 hours after administration of cytotoxic chemotherapy. Transient bone pain is usually mild to moderate, but often more pronounced than that seen with filgrastim.

CANCER DRUG DEVELOPMENT

The only proven way to improve the success of cancer treatment involves testing new agents, higher doses, novel combinations of drugs, or unique ways of administering treatment. Over the past few decades, clinical trial designs have become increasingly sophisticated and therefore more reproducible. Since gynecologic cancers are relatively uncommon, most landmark phase III studies are conducted within large collaborative groups such as the Gynecologic Oncology Group (GOG). Occasionally, there are astonishing successes. For example, metastatic gestational choriocarcinoma has gone from a uniformly fatal diagnosis to being routinely cured with combination chemotherapy. More commonly, there is a gradual improvement in extending the length of survival that takes years to realize.

The identification of a new and active anticancer drug is a long, complicated, expensive process. Promising drugs are first identified by demonstrating success in cancer cell lines or in animals inoculated with tumor. Next, drugs are subjected to detailed preclinical toxicology tests in animals. After preclinical steps are completed, novel agents proceed through four phases of clinical testing.

Phase I trials use a dose-escalating design to determine the dose-limiting toxicity, maximally tolerated dose (MTD), and pharmacokinetic parameters of the drug. Groups of three to six patients with a variety of tumor types are enrolled at each dose, depending on the amount of toxicity that can be tolerated. In a phase I trial, detecting a tumor response is not critical, since enrolled patients have typically completed extensive prior therapy. However, observed responses would encourage further disease-specific phase II trials.

After the recommended dose and treatment schedule have been defined in a phase I trial, the regimen can proceed to phase II. The primary goal of this trial type is to define the actual response rate in patients with a specific cancer type. Usually a measure of disease (MOD) is required to allow accurate determination of a complete response, partial response, stable disease, or progression. Typically, patients enrolled in phase II trials have received only one prior chemotherapy regimen. This allows for a reasonable chance of response, compared with subjects in phase I studies. Secondary end points of phase II trials include determination of the "progression-free interval", cumulative incidence of dose-limiting toxicity over multiple cycles, and overall survival.

When a promising regimen is identified in phase II, it may then progress to phase III. These randomized trials are designed to directly compare the investigational drug with existing standard regimens in a particular stage and type of cancer. Phase III trials generally require a minimum of 150 patients per arm to provide adequate statistical precision.

In general, patients should be strongly encouraged to participate in appropriate phase I, II, and III clinical trials. By doing so, their options for treatment are expanded. In addition, the results of such studies are the primary method to improve the outcomes of those women diagnosed with gynecologic cancer in the future.

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PRINCIPLES OF RADIATION THERAPY: INTRODUCTION

Following the discovery of x-rays in the waning years of the 19th century, the biologic effects of ionizing radiation (IR) were quickly recognized. Since then, radiation therapy (RT) has been used, either alone or in conjunction with other modalities, to treat a variety of conditions, both malignant and benign. Over the last few decades, technological innovation in medical imaging equipment and computers has helped tremendously in RT planning and delivery.

Radiation therapy can be delivered by external beam therapy; internal placement of radionuclide sources, termed *brachytherapy* ; or by instillation of radionuclide solutions. These forms play significant roles in the treatment of various gynecologic malignancies (Table 28-1). For example, external beam therapy and brachytherapy play major roles in the primary management of inoperable cancers of the cervix, vagina, and vulva. Additionally, they may be recommended as adjuvant treatment in the postoperative setting if there is a high probability of regional recurrence. For uterine malignancies, external beam therapy or brachytherapy may be recommended for adjuvant posthysterectomy treatment, or occasionally can be used as a primary modality for inoperable tumors. For epithelial ovary cancer, the indications for RT are minimal. Similarly, there currently is a limited role for external beam therapy in the management of ovarian germ cell tumors and gestational trophoblastic neoplasia (Soper, 2003). Radiation therapy is used frequently in the relief of symptoms caused by metastasis of any gynecologic cancer. Pain, bleeding, spinal cord compression, bronchial obstruction, and brain metastasis can be effectively palliated.

Table 28-1 Role of Radiation Therapy in the Management of Gynecologic Cancers

Intent	Site
Curative	Cervix, vulva, vagina
Adjunctive to surgery	Cervix, vulva, vagina, uterus
Palliative	Metastasis causing symptoms: bleeding, pain, obstruction

RADIATION PHYSICS

Electromagnetic Radiation

Photons and gamma rays are the two most common types of electromagnetic radiation used in RT. Both can be considered as *electromagnetic waves* or as discrete particles (quanta) of energy. This duality is described by the wave-particle theory of quantum physics, which explains that energy can be transferred either by waves or particles. The main distinction between photons and gamma rays lies in their origin. *Photons,* also known as *x-rays,* are produced when a stream of electrons collides with a high-atomic-number target like tungsten. Photons are used in external beam therapy and are produced by linear accelerators, which are described later. In contrast, gamma rays originate from unstable atom nuclei and are emitted during decay of radioactive materials.

Particle Radiation

Whereas electromagnetic waves are defined by their wavelengths, radiation particles are defined by their masses. For clinical use, they include electrons, neutrons, protons, helium ions, heavy charged ions (e.g., carbon, neon, and argon), and pi mesons. Except for electrons, which are in daily clinical use, only a few institutions in the world have the capability to investigate the other particles for cancer therapy. All of these particles are produced by linear accelerators or other high-energy generators designed for physics

research.

Particle radiation is usually delivered by external beam and each particle type has specific biologic and physical properties. *Electrons* are negatively charged and due to their superficial depth-dose characteristics are only suitable for the treatment of cancer near the skin surface, such as inguinal lymph nodes.

Neutrons carry no electrical charge, and therefore transfer energy by nuclear disintegration or by colliding directly with a hydrogen nucleus. Since a high content of hydrogen is found in fat tissues, the energy deposition into fat with this form of radiation is higher than in muscles. This explains the high incidence of fat loss and subcutaneous fibrosis associated with pelvic neutron therapy. Neutron beam therapy is particularly effective for slow-growing tumors and has been used in the treatment of salivary glands, sarcoma, and prostate cancers.

Protons and *helium ions* characteristically deposit the highest energy dose near the maximum depth of beam penetration, with a sharp dose taper after that peak. They are used in the treatment of rare tumors such as uveal melanoma, chordoma, and chondrosarcoma. Finally, h*eavy charged ions* and *pi mesons* are being investigated for the treatment of a variety of tumors.

Radionuclides

Radionuclides, also called radioisotopes, undergo nuclear decay and can emit: (1) positively charged alpha particles, (2) negatively charged beta particles (electrons), and (3) electromagnetic gamma rays. Radionuclides commonly used in gynecologic oncology are commercially available as sealed sources such as cobalt, cesium, iridium, gold, and iodine, or as unsealed solutions of strontium, iodine, or phosphorus (Table 28-2).

Table 28-2 Physical Properties and Clinical Use of Selected Radionuclides

Element	Radiation Energy in MeV	Half-Life	Clinical Use
Cesium-137	0.6	30 years	Brachytherapy
Iridium-192	0.4	74 days	Brachytherapy
Cobalt-60	1.2	5 years	Brachytherapy
Iodine-125	0.028	60 days	Brachytherapy
Phosphorus-32	1.7	14 days	Intraperitoneal instillation
Gold-196	0.4	2.7 days	Intraperitoneal instillation
Strontium-89	1.4	51 days	Diffuse bone metastasis

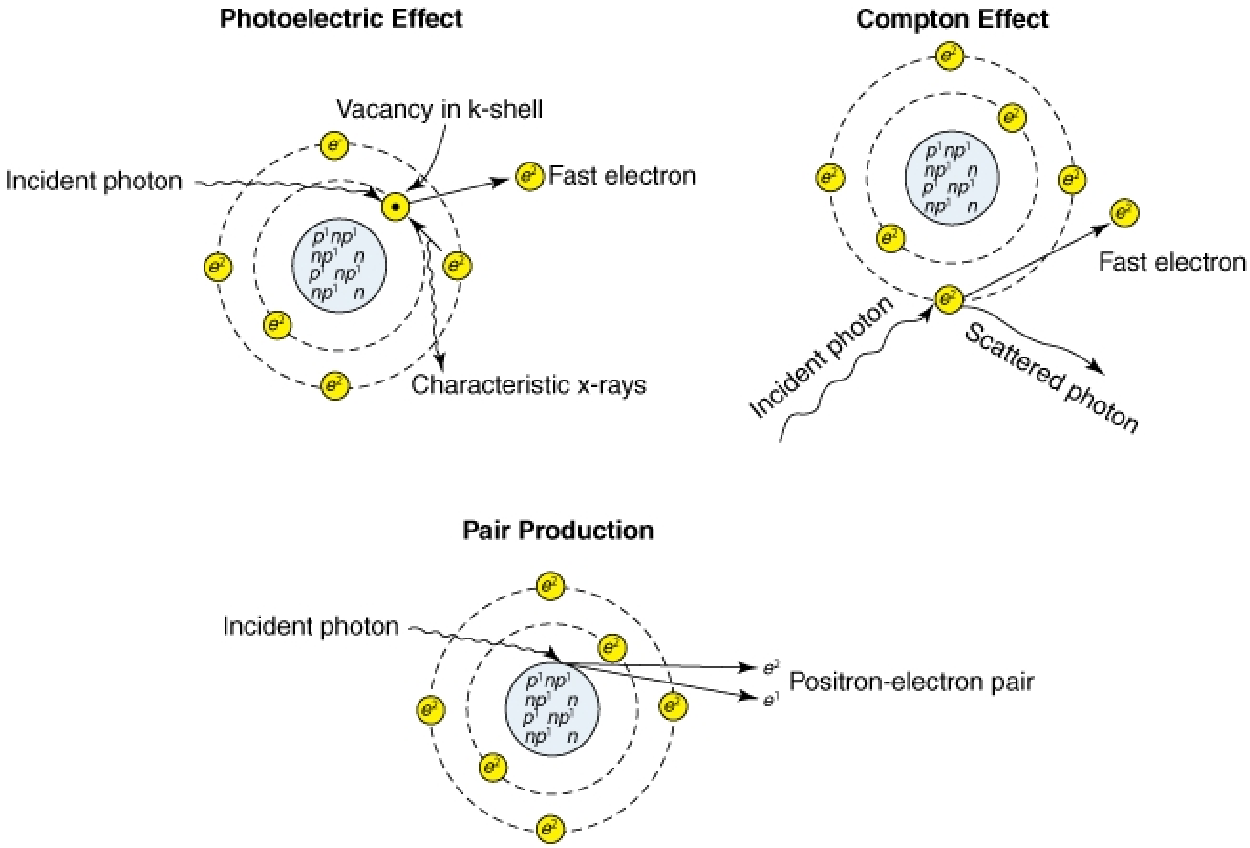
MeV = million electron volts.

Electromagnetic Radiation Energy Deposition

When electromagnetic radiation is used in daily clinical practice, it interacts with tissues, and energy is transferred to those tissues. Importantly, the impacting energy, also called *incident energy* , causes the formation of ions by dislodging electrons from atoms within these tissues. During this ionizing process, energy is transferred to fast electrons, which then interact with the surrounding molecules to initiate the biologic process of radiation damage.

There are three mechanisms involved in the energy transfer: *photoelectric effect, Compton effect,* and *pair production (PP)* (Fig. 28-1). The *photoelectric effect* is dominant when the incident energy is low. The effect causes ejection of an orbiting electron from its shell, and this ejected "fast"-electron kinetic energy is deposited into tissues. After ejection, this vacancy is filled by an electron from an outer orbiting shell with the emission of a characteristic x-ray, which has little biologic effect. The photoelectric effect is proportional to the third power of the atomic number (Z) of the absorbing medium and is inversely related to incident energy.

FIGURE 28-1



Both photoelectric and Compton effects result in the creation of fast electrons which initiate the biologic process of radiation damage. The pair production process involves the interaction of incident photon and nuclear forces to produce a positron-electron pair. When a positron combines with a free electron in tissues, two photons are created. *(Redrawn from Hall, 2003, with permission.)*

Radiologists take advantage of the photoelectric effect in the creation of radiographs. For example, when a pelvic radiograph is obtained for diagnostic purposes, a low x-ray energy is used. Because bones have a higher Z number than muscles and fat, they absorb more energy and appear brighter on radiographs. As a result, bony structures are clearly seen, whereas the muscle and fat tissues are barely identified. In contrast, when a verification pelvic film is taken during a radiation therapy course that uses a high-energy photon beam, the contrast between the bones and soft tissues is less evident.

The *Compton effect* is seen with high-energy photons used clinically in RT. It occurs when the incident photon energy is much larger than the binding electron energy with which the photon interacts. In this interaction, part of the photon energy is transferred to the electron, which is ejected from the orbiting shell. This "fast" electron initiates the biological chain of events leading to DNA damage.

Pair production occurs when a photon beam with very high energy interacts with the electromagnetic field of the nucleus. The result is formation of a *pair* comprised of a negatively charged electron and a positively charged positron. When the positron slows and interacts with a negatively charged electron, there is mutual annihilation, and two photons going in opposite directions are produced. These photons interact with the tissues to transfer energy and cause biologic damage.

Depth-Dose Curve

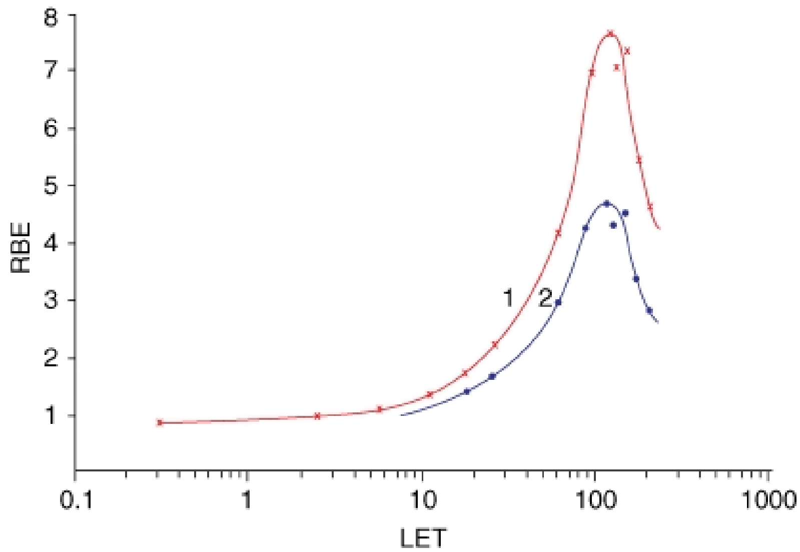
With high-energy photons, maximum energy is deposited below the tissue surface, and beyond this point, the dose gradually tapers

as the energy is absorbed by the deep surrounding tissues. This explains the so called *skin-sparing effect* of high-energy photons. In contrast, with electron beam therapy, the maximum dose lies much closer to the surface and the dose distribution has a steeper taper. For this reason electron beam therapy is preferred for targets which are close to the skin surface such as disease metastatic to the inguinal lymph nodes.

Linear Energy Transfer and Relative Biologic Effectiveness

When a radiation beam interacts with tissue, ionizing events occur along the path of energy transfer. The rate of energy deposition along this path is called *linear energy transfer* or LET, which is expressed as kiloelectron volts (keV) per micrometer. Photons, gamma rays, x-rays, electrons, protons, and helium ions are classified as low-LET radiation since the ionizing events tend to be sparse. In contrast, high-LET radiation, such as heavy particles (fast neutrons, heavy charged ions, and pi mesons), creates dense clusters of ionization and as a result, are more biologically damaging. To compare the biologic effectiveness of different radiation types, a parameter called *relative biologic effectiveness* (RBE) is used. It is defined as the ratio of photon to neutron doses used to achieve a specified biologic end point. Therefore, it should be noted that RBE values depend on the chosen biologic end points under consideration. As the LET increases, RBE also increases and reaches a peak at 100 keV/micron (Fig. 28-2).

FIGURE 28-2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Linear energy transfer (LET) as a function of relative biologic effectiveness (RBE). RBE reaches its maximum at about 100 keV/micron and varies depending on biologic endpoints. Curves 1 and 2 refer to cell survival of 80 percent and 10 percent, respectively. *(Adapted from Barendsen, 1968, with permission.)*

Radiation Unit

The biologic effect of ionizing radiation (IR) correlates well with the amount of energy transferred to tissues. Therefore, in the practice of radiation oncology, quantification of the absorbed radiation dose delivered to tissues is essential. In older terminology the unit of measure, called *rad* , was used to describe the absorbed dose. One rad, literally *radiation absorbed dose* , is defined as 100 erg/g. Currently, the Standard International unit for an absorbed dose is gray (Gy). One Gy equals 100 rad or 1 joule/kg. Clinically, the radiation doses for curative and palliative treatments are 70 to 85 Gy and 30 to 40 Gy, respectively.

Radiation Equipment

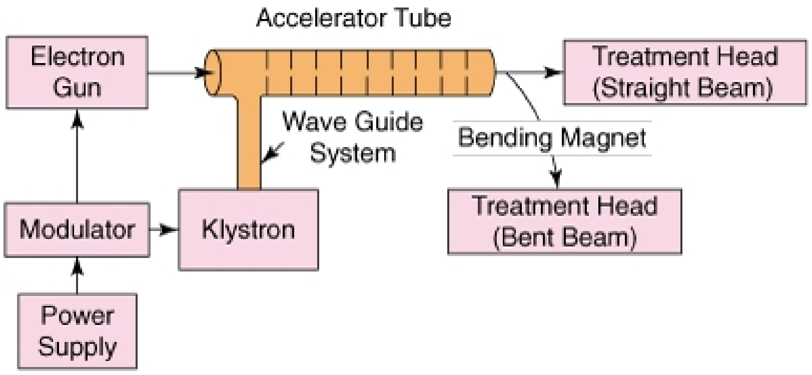
LINEAR ACCELERATOR (LINAC)

As technology has advanced, the armamentarium for deep radiation delivery has vastly expanded from the kilovoltage to

megavoltage unit. Among the many types of photon-producing megavoltage units, the linear accelerator, also called a *linac* , is the one that is widely used throughout the world to deliver external beam radiation therapy.

A linac can produce both photon and electron beams for therapeutic use (Fig. 28-3). The electrons are produced by an electron gun and are injected into a linear tube where they are accelerated by electromagnetic waves produced by a klystron. A modulator then synchronizes the pulsed injections of electrons and electromagnetic waves into the accelerator tube. In the *photon-therapy mode* , indicated for deep-seated tumors, the accelerated electron beam is guided to a metal target via a beam steering system producing photons with heterogeneous energies. Before clinical use, this beam hits a flattening filter to make its intensity uniform (Fig. 28-4). In contrast, in the *electron-therapy mode* for superficial lesions, the electron beam strikes a scattering foil instead of the metal target.

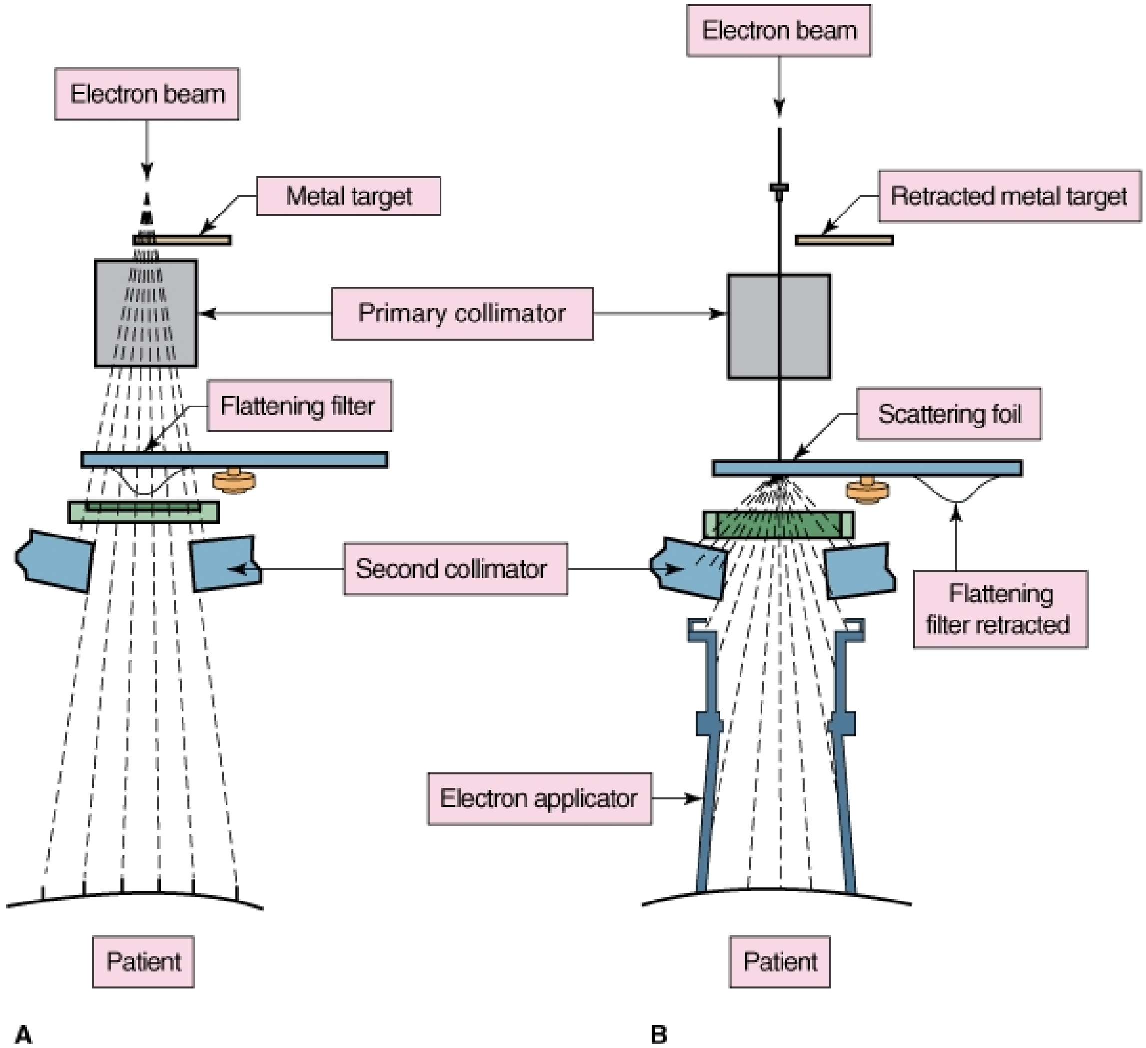
FIGURE 28-3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Block diagram of a linear accelerator. *(Modified from Khan, 2003, with permission.)*

FIGURE 28-4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

To create radiation beams with uniform dose distribution across the treatment fields, linear accelerators modify beams with filters and foils. In the photon therapy mode **(A),** the electron beam strikes a flattening filter. In the electron therapy mode **(B),** it hits a scattering foil. *(Redrawn from Karzmark, 1981, with permission.)*

The unit used to describe the energy of a photon beam is MV (million volts). The unit for electron beam energy is expressed in MeV (million electron volts). Customarily, a linac is designated by a number corresponding to the highest energy of the electron beam available. For example, the maximum energy of the electron beam produced by a linac 18 is 18 MeV.

Figure 28-5 displays a linac with four components: stand, gantry, treatment head, and couch (Varian Inc., Palo Alto, CA). The power source, modulator, and klystron are located in the stand. The electron gun, accelerator tube, and bending magnets are housed in the gantry. The treatment head is mounted on the gantry and contains the metal target, flattening filter, scattering foil, and collimators, which shape the treatment fields (see Fig. 28-4). The gantry, treatment head, and treatment couch can all rotate 360 degrees. Thus, the mobility of the basic components of the linac allows the use of multiple fields and angles to achieve optimal dose delivery to the tumor while minimizing the exposure of normal tissues.

FIGURE 28-5

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photograph of a linear accelerator currently in use at the University of Texas Southwestern Medical Center. The patient lies on the treatment couch. The gantry (G), couch (C), and head (H) can all rotate and allow radiation beams to reach the targets through different angles. (*Courtesy of Dr. Geoffrey Zhang.*)

COBALT MACHINE

Although linacs are widely installed for cancer treatment around the world, cobalt machines are still being used for external beam therapy in a very few centers in the U.S. and in most developing countries. The unstable radioactive cobalt-60 isotope undergoes nuclear decay by emitting 1.17 MV and 1.33 MV gamma rays. However, this isotope's half-life is short (5.2 years), and thus the source requires frequent replacement, every 4 to 5 years.

RADIATION BIOLOGY

Direct versus Indirect Effects of Ionizing Radiation

About 70 percent of the ionizing effects of low-LET electromagnetic radiation, such as photons used in clinical settings, are *indirect.* Energy is transferred from the radiation to the target through chemical intermediates. Tissues are mostly formed of water. The interaction between electromagnetic radiation and water molecules produces the H_2O^+ ion, which then reacts with water to form a free radical, the hydroxyl radical ($OH^{\text{â€“}}$). Because of this radical's unpaired electron, it is highly reactive and easily transfers energy to the target tissue. It is this interaction between hydroxyl radicals and DNA molecules that leads to biologic damage. However, for the chemical changes within the DNA to be permanent or "fixed", free radicals must interact with oxygen. Without the presence of oxygen, this reaction cannot occur. This is the basis for the so called "oxygen fixation" hypothesis. Ninety-five percent of the energy deposited by electromagnetic radiation in tissues occurs within 4 nm of the ionization track, that is, about two DNA molecule diameters.

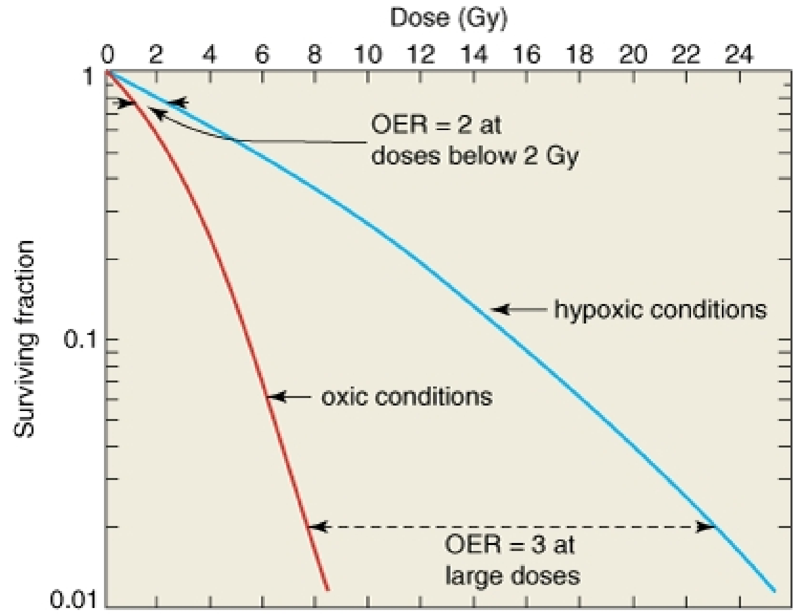
In contrast, particle radiation (protons, neutrons, electrons, and heavy ions) produces ionizing events by *direct* collision with their

biologic targets.

Importance of Oxygen

As noted above, the presence of oxygen is critical to the response of mammalian cells to low-LET radiation. The oxygen enhancing ratio (OER) is the ratio of doses needed to achieve the same cell survival fraction in hypoxic and oxic environments. The OER value depends on the type of IR. For low-LET photons, the OER is approximately 3. This means that the dose needed to achieve a defined biologic effect on a population of hypoxic cells is 3 times higher than the one used to have the same results in oxic conditions. In contrast, for high-LET heavy particles like neutrons, the OER is about 1.5. This implies that tumor hypoxia becomes less relevant with high-LET, and therefore high-RBE radiation (Fig. 28-6).

FIGURE 28-6



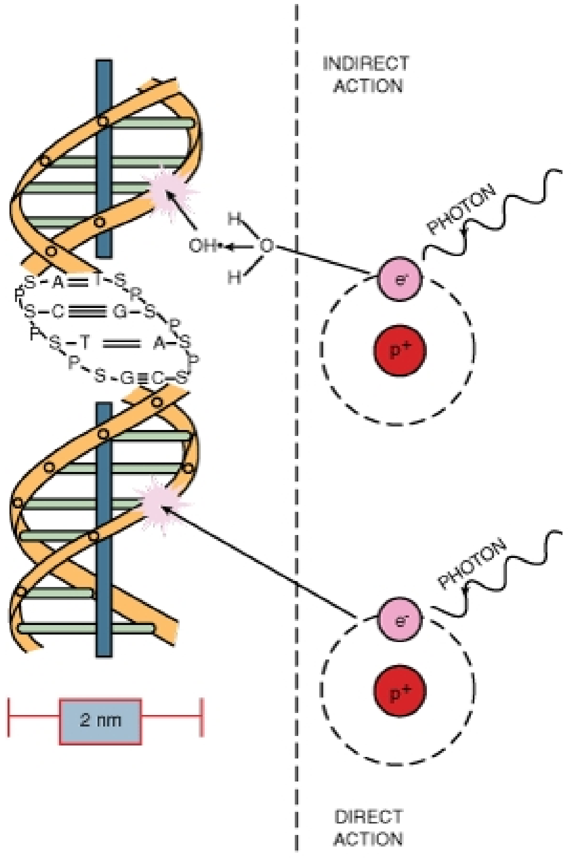
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Cells in an oxic environment are sensitive to radiation, that is, their surviving fraction is decreased, compared with that in hypoxic conditions. The oxygen enhancing ratio (OER) is the ratio of doses needed to achieve the same surviving fraction in hypoxic and oxic conditions. *(Redrawn from Hall, 2003, with permission.)*

DNA Molecule as Ionizing Radiation's Target

There is strong evidence to indicate that the target for the biologic effect of IR on mammalian cells is the DNA molecule (Fig. 28-7). DNA injuries involve the strands, bases, and cross-links (DNA-DNA and DNA-protein). The hallmark of intracellular radiation damage is the breaking of the DNA molecule strands. Single- (SSB) and double-strand breaks (DSB) may occur. Single-strand breaks develop when only one strand is damaged and are easily repaired. Currently, radiation biologists agree that the most important lesion is the DSB. Double-strand breaks effectively create DNA fragmentation when two or more breaks are formed in opposite locations of the DNA ladder. When cells attempt to repair the strand breaks, the DNA pieces may rejoin incorrectly leading to gene translocation, mutation, or amplification. Cell death can follow, and increasing numbers of DSBs have been positively correlated with cell death.

FIGURE 28-7



Direct and indirect actions of radiation. In direct action, an electron that results from absorption of a photon interacts with DNA. With indirect action, an electron produced from photon absorption interacts with water to create a hydroxyl radical, which subsequently interacts with DNA. A, T, G, C = base nucleotides; P = phosphorus; S = sugar. *(Redrawn from Hall, 2000, with permission.)*

Cell Death

After ionizing radiation (IR) exposure, cells sustain damages triggering competing death and survival signals. How cells deal with that stress will determine their ultimate fate. A cell is considered biologically dead when it has lost its reproductive capacity. The two main cell death pathways are apoptosis and mitotic death.

APOPTOSIS

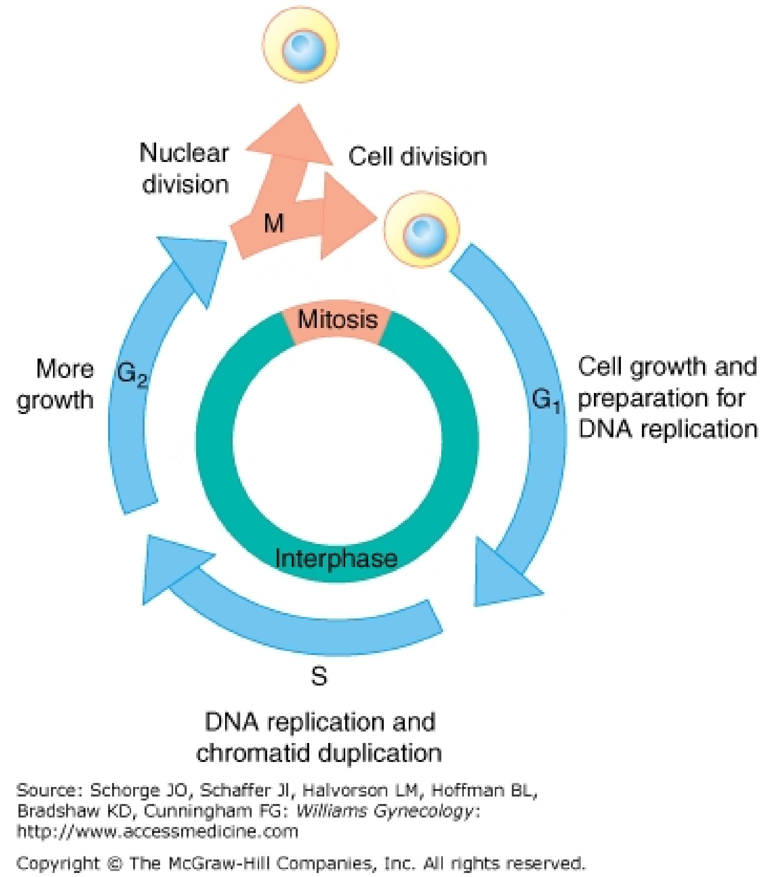
Apoptosis, derived from a Greek word which means *dropping of leaves from a tree* , is also known as programmed cell death or interphase death. It occurs naturally in normal organisms to limit cell proliferation and maintain homeostasis. Dysregulation of the normal apoptotic process is believed to play a role in carcinogenesis as well as numerous other pathologic conditions.

After an intracellular stress, such as IR-induced irreparable DSB, a series of events develop rapidly within a few hours and cell membrane blebbing, formation of apoptotic bodies in the cytoplasm, chromatin condensation, nuclear fragmentation, and DNA laddering can be seen (Okada, 2004). Apoptotic tendency is seen in lymphocytes, spermatogonia, salivary glands, and some tumors that are responsive to IR. Such tissues are believed to have a "pro-apoptotic phenotype". Conversely, cells with "anti-apoptotic phenotype" are resistant to IR. The clinical significance of IR-induced apoptosis resides in the assumption that the factors that shape the death pathways determine the intrinsic cellular radiation sensitivity.

MITOTIC DEATH

A cell cycle has four phases: G_1 , S, G_2 , and M (Fig. 28-8). Cells with damaged DNA are frequently blocked at the G_2 /M checkpoint from moving along the cell cycle to the mitotic (M) phase. If these cells enter the M phase prematurely, before DNA repair is complete and with aberrant chromosomes, they will form multinucleated giant cells with uncondensed chromosomes and will die attempting to complete the next two to three mitotic cycles. Therefore, a mitotic death is delayed in contrast with the more immediate apoptotic death.

FIGURE 28-8



Mammalian cell cycle. DNA replicates in the S phase, whereas in the M phase, the cell divides.

Cells, such as those in ataxia telangiectasia, have defective G_1 /S and G_2 /M checkpoints, allowing cells with damaged DNA to move along the cell cycle. As a result, they are exquisitely sensitive to IR. Human papillomavirusâ€"positive cervical cancer cells with oncoproteins E6 and E7 have also been found to have a defective G_1 /S checkpoint and are capable of developing genomic instability and apoptosis. Moreover, exposed to neocarzinostatin, an agent which causes SSBs and DSBs in DNA, cervical cancer cells demonstrate a strong G_2 /M arrest and a higher percentage of mitotic death when compared with normal human keratinocytes (Banuelos, 2003).

Cell Repair

After IR exposure, cells which survive will repair their damage. Two types of repair have been described: sublethal damage repair (SLDR) and potentially lethal damage repair (PLDR). Currently, the molecular mechanisms of SLDR and PLDR are unknown. Both SLDR and PLDR have been observed in normal and tumor tissues.

SUBLETHAL DAMAGE REPAIR

When a radiation dose is split into two or more fractions and a few hours separate each fraction, cells have time to repair their

damage, and their rate of survival increases. This type of repair is typically completed within 6 hours after IR. During SLDR, a number of characteristic processes have been noted. Following the initial *repair* of sublethal damage, *reassortment* begins. In a tumor, proliferating cells are located at different phases of the cell cycle. When exposed to IR, those cells which happen to be at G_2 /M phase are most sensitive to IR and are killed. During reassortment, surviving cell populations restart their progression through the mitotic cycle. In this manner, all cells within a tumor reassort or redistribute themselves into different phases of the cycle. Following reassortment, mitosis begins again. The last process seen in SLDR is *repopulation* , the tissue response to replenish the cell pool (Trott, 1999).

POTENTIALLY LETHAL DAMAGE REPAIR

After IR exposure, certain environmental conditions, when applied to the irradiated tissues, can lead to increased cell survival. Conditions such as decreased nutrients or lower temperatures, which are suboptimal for growth, allow more time for repair of DNA damage. In these settings, the ability of cells to repair the IR-induced damages correlates with their radiation sensitivities (Kelland, 1988).

The Four R's of Radiation Biology

In addition to cellular repair, reassortment, and repopulation, the fourth "R" of radiation biology theory is a phenomenon called reoxygenation. A tumor cell population is composed of oxygenated and hypoxic components. Those cells that are located within 100 microns of blood capillaries are oxygenated, and those beyond 100 microns are hypoxic. After a dose of IR, the oxygenated cells die because they are radiosensitive. As a consequence, the tumor shrinks, allowing for hypoxic cells to be repositioned within the range of oxygen diffusion from the blood capillaries. Thus, these previously hypoxic cells now become oxygenated and die when another dose of IR is delivered.

Cell Survival Curve

The survival curve of mammalian cells exposed to low-LET IR illustrates the relationship between the IR dose and the proportion of the cell population that retains the ability to proliferate. Among the many models, the one called linear-quadratic has been adopted to explain this relationship. The curve is composed of two parts. The initial linear portion of the curve reflects that the probability of cell death is proportional to the IR dose, whereas the curved quadratic portion indicates that the probability is proportional to the square of the dose. The components of the cell survival curve therefore are expressed as alphaD and betaD^2 . The dose is denoted by "D", but alpha and beta are constants. At the dose D = alpha/beta, there is an equal contribution to cell death from the linear and quadratic parts.

In contrast, when high-LET IR, such as neutron therapy, is used, the shape of the curve is straight.

Clinical Implication of the Alpha:Beta Ratio

Not all normal tissues respond similarly to IR. Those that manifest reactions to IR within a few days to weeks after IR initiation are categorized as *early responding* . Examples are tissues with a high proliferation rate like bone marrow, reproductive organs, and gastrointestinal tract mucosa. Their alpha:beta ratio values are high and are reflected by the steep early slope on the cell survival curve. In contrast, *late responding* tissues only show clinical reactions weeks to months after completion of a course of radiation therapy. It is postulated that late responding tissues are composed of cells in G_0 , the quiescent stage. Examples are the lung, kidney, spinal cord, and brain.

By using multiple small dose fractions, the alpha component is amplified. Thus, with treatment protraction, there is an opportunity to decrease acute reactions. For patients who have IR delivered to the abdomen, in which the mucosal tissues are early responding, treatment protraction is preferred. Alternatively, late responding tissues are slow to respond by proliferative reaction and their alpha:beta ratio values are low. A low ratio value means that the cell survival fraction is markedly decreased when the dose per fraction is high. It takes more time to repair sublethal damage in late-responding than in early-responding tissues. Therefore, the use of high-dose-per-fraction RT can easily lead to severe late complications. Accordingly, there is a high incidence of myelitis if the spinal cord receives a high IR dose in a short period of time, that is, a large fraction dose.

RADIATION THERAPY

External Radiation Therapy

External radiation therapy is indicated when an area to be irradiated is large, for example the fields covering a cervical cancer and the draining nodes. The basic tenet of radiation therapy is to maximize the tumor dose while minimizing the damage to the surrounding normal tissues. To attain this goal, the radiation oncologist must know the precise extent of the cancer to be irradiated and its relationship to the surrounding normal tissues.

This process begins with a review of the patient's cancer imaging. Modern imaging tools include computed tomography (CT), magnetic resonance (MR) imaging, and functional imaging techniques such as nuclear MR imaging/spectroscopy, positron emission tomography (PET) and single-photon emission computed tomography (SPECT). These have aided the radiation oncologist tremendously in defining three-dimensional tumor and healthy tissue volumes (Chapman, 2001; Kwee, 2004, Zakian, 2001).

Following image review, *radiation therapy simulation* is performed to delineate the anticipated therapy fields prior to an actual treatment session. During this process, patient positioning and treatment fields are defined, and radiation blocks are designed to shield normal tissues. Both x-ray machines and CT scanners can be used in simulation. X-ray machine simulators are currently used for simple cases such as palliative planning for metastatic cancer to the brain, bones, and other organs. For most patients, a CT simulation is required using a CT scanner with additional equipment that aids treatment planning.

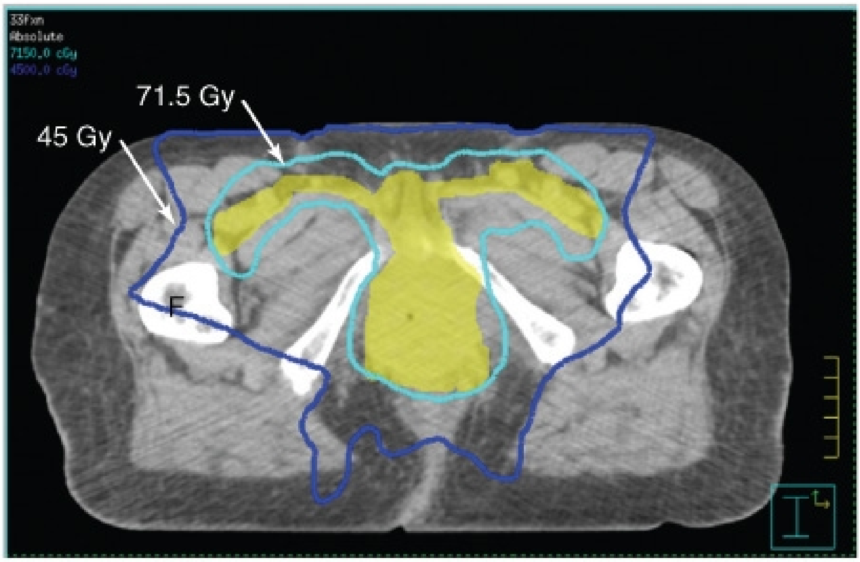
During simulation, the patient is placed in position for treatment, and a CT scan of the area of interest is performed. On each of the CT scan slices, the radiation oncologist delineates by hand the target volumes that are to receive a tumoricidal dose, as well as those at risk for early and late radiation complications. With these specifications, the radiation dosimetrist employs treatment planning software. During this step, the optimal arrangement of the radiation beams, in the case of external radiation therapy, or radioactive sources, in the case of brachytherapy, is developed to achieve treatment goals. This step is called *dose optimization* .

One tool that is particularly helpful in the radiation planning and optimization process is the dose volume histogram. This imaging tool displays the entire dose distribution for the cancer and normal structures. Three-dimensional conformal radiation therapy (3D-CRT) dose distributions are generated for the radiation oncologist to review, adjust, and finally approve. The final chosen plan is checked by a radiation physicist who ensures that the physical and technical details can be implemented.

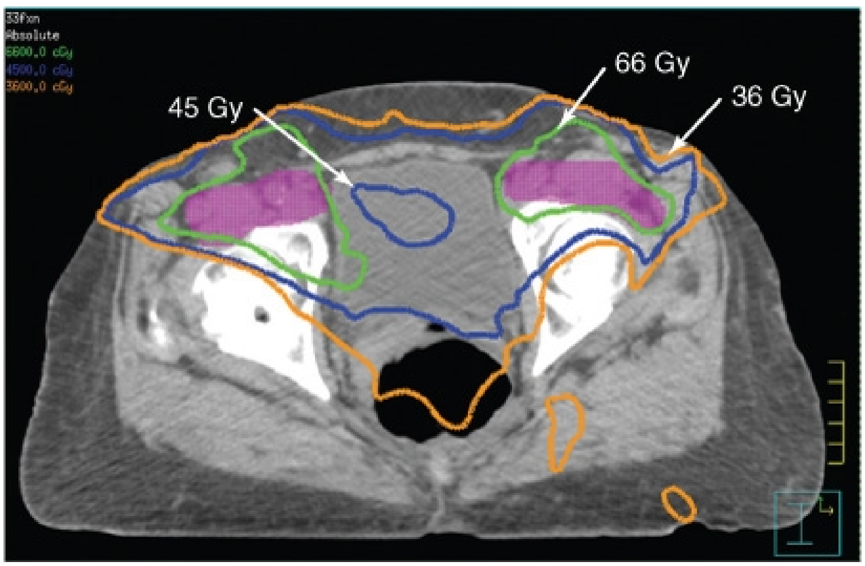
In an effort to further improve the conformality of the dose distribution, especially around concave-shaped targets, a more advanced 3D-CRT planning system, called *intensity-modulated radiation therapy (IMRT)* , is used. As a result of this improved conformality, IMRT has the potential to decrease bowel and bladder toxicity during pelvic IR therapy (Heron, 2003).

In this system, the intensity of the radiation beams is modulated or changed according to the dose constraints or limits assigned to different regions within the irradiated fields (Fig. 28-9). The radiation oncologist defines the dose specifications to different areas. Then, the computer, by a reiteration or trial process, comes up with an optimal solution. This type of treatment planning is called *inverse planning.* In other words, the radiation oncologist first defines the doses to be delivered to tumor and normal tissues. This differs from *forward planning* . For example, in the forward planning for the more common pelvic malignancies, the radiation oncologist chooses an a priori standard pelvic four-field technique.

FIGURE 28-9



A



B

IMRT dose distribution in a patient with stage T4N2M0 cancer of the vulva. This technique allows for the delivery of tumoricidal doses to the vulva and inguinal nodes while minimizing delivery to normal tissues such as rectum, bladder, and bones. **A.** Doses to the vulva and femoral heads are shown **(arrows)** . The yellow area displays the actual vulvar cancer and inguinal lymph nodes. **B.** Doses to vulva, rectum, and femoral heads are shown **(arrows)** . Pink shading displays the inguinal nodes.

For quality assurance purposes, there is weekly or sometimes daily film verification. The radiation oncologist compares the portal

images taken on the treatment machine with the original simulation films. If deviations are noticed, adjustments are made. The radiation oncologist also monitors the patient weekly for untoward treatment side effects. If severe acute complications develop, treatment plans may be revised or a break in treatment may be warranted.

Brachytherapy

Brachytherapy (radiation implant) means treatment at a short distance. During this therapy, sealed or unsealed radioisotopes are inserted or instilled into the cancer or its immediate vicinity. Radiation doses decline sharply with increasing distances from the radioactive source. Accordingly, brachytherapy (BT) is indicated only when the cancer volume is small, less than 3 to 4 cm in greatest dimension. For this reason, BT is typically practiced after external radiation therapy has decreased the tumor size.

INTRACAVITARY, INTERSTITIAL, AND INTRAPERITONEAL BRACHYTHERAPY

During *intracavitary BT* , the applicators holding the sealed sources, such as cesium, are inserted into a body cavity such as the uterus. Alternatively, *interstitial BT* requires the placement of catheters or needles directly into the cancer and surrounding tissues. The typical source used in interstitial BT is iridium. Unsealed sources, such as phosphorus and gold, are available as solutions for instillation into peritoneal cavities.

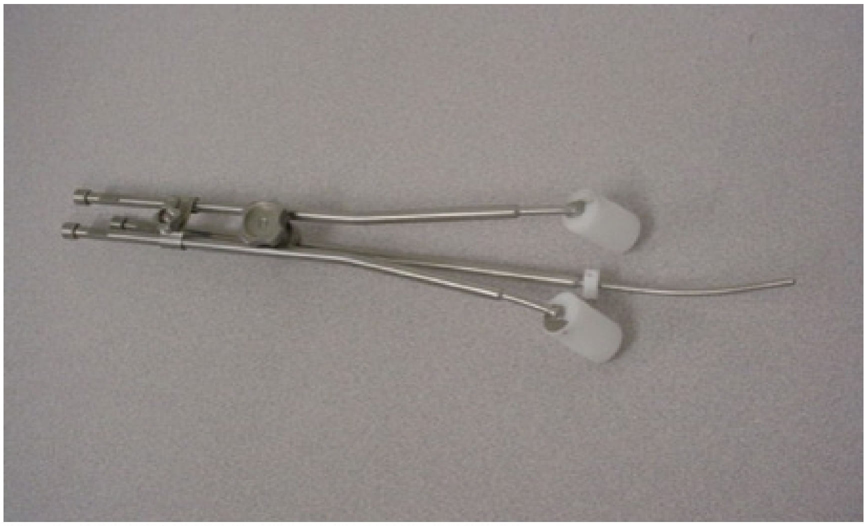
TEMPORARY AND PERMANENT BRACHYTHERAPY

In *temporary BT* , the radioisotopes are removed from the patient after a period of time ranging from minutes to days. All intracavitary and some interstitial implants are temporary. In *permanent BT* , the radioisotopes are left to decay within the tissues. The time for the delivery of the absorbed dose varies depending on the isotopes used and ranges from 1 week with gold to 6 months with iodine.

EQUIPMENT

For routine gynecologic intracavitary implantation, standard equipment includes an applicator, called a *tandem* , which fits into the uterus, and a pair of vaginal applicators, which are known as *ovoids* or alternatively, called *colpostats* (Fig. 28-10). Tandems have different curvatures to adapt to varied uterine shapes. Similarly, plastic caps can be fitted to ovoids to adapt to varied vaginal anatomy. The tandem and ovoid device (T&O) is inserted under general anesthesia or conscious sedation. Following placement, radioactive sources can then be loaded into the tandem and ovoids either manually or remotely. In gynecologic oncology, brachytherapy with T&O is indicated for cancer of the cervix and endometrium.

FIGURE 28-10



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Typical tandem and ovoids (colpostats) used for cervical cancer brachytherapy. The device is inserted into the endometrial cavity and vagina. An iridium radioactive source is loaded into the device via a remote control mechanism. (*Courtesy of Dr. Geoffrey Zhang.*)

In contrast, for temporary interstitial implantation, flexible plastic catheters or metal needles are surgically placed into the target tissues. These are then afterloaded with iridium seeds. To achieve an optimal dose distribution, the catheters or needles should stay firmly in place. For this reason, a perineal template is often used. Although used less frequently than T&O, templates are suitable in the management of patients with advanced cancer, with suboptimal anatomy for T&O application, and with selected recurrent cancer.

MANUAL VERSUS REMOTE AFTERLOADING

During brachytherapy, once the holding devices for the radioactive sources are optimally positioned, the sources are inserted. Previously, these sources were carried in a shielded cart to the patient's room, loaded into the patient, and then removed and replaced in a storage room following treatment. This *manual afterloading* method increased hospital staff radiation exposure. For this reason, a *remote afterloading* approach was developed and is commonly practiced today. This remote control system delivers through connecting cables a single miniaturized iridium or cobalt source to the holding devices previously inserted into the patient. When IR is actually delivered, personnel are outside the patient's treatment room. Following treatment, the radioactive source is automatically retracted back into the safe.

LOW DOSEÂ€“RATE VERSUS HIGH DOSEÂ€“RATE THERAPY

Traditionally, low doseâ€“rate (LDR) brachytherapy is delivered over the course of many days and requires patient hospitalization. Over the last few decades, however, high doseâ€“rate (HDR) brachytherapy has become more popular. With this technique, treatment is shortened to minutes. Low dose rate is defined as dose rates from 0.4 Gy to 2 Gy/hr, and HDR as rates higher than 12 Gy/hr. For example, in an intracavitary implant for cervical cancer with an LDR technique, a dose of 30 to 40 Gy is given over several days continuously. In contrast, in an HDR technique, an equivalent dose can be delivered in 3 to 5 weekly fractions. The dose per fraction is 6 to 8 Gy and can be given in 10 to 20 minutes.

The radiobiology differences between LDR and HDR brachytherapy are based on the dose-rate effect. As the dose rate increases there are: (1) decreased cell survival of tumor and early-responding normal tissues due to the lack of tissue injury repair, and (2) increased damage to the late-responding normal tissues. Therefore, to avoid late complications, the number of fractions is increased from 1 to 2 in LDR to 3 to 6 in HDR brachytherapy. Furthermore, the total tumor dose delivered in HDR brachytherapy of the cervix is lower than the one used in LDR (Nag, 2000). This dose is divided into brief fractions that avoid lengthy inpatient hospitalization and minimizes patient immobility and thromboembolic events. Long-term analysis has not shown any striking differences in local tumor control or in late complications in patients with cervical cancer treated with either HDR or LDR brachytherapy (Arai, 1991; Hareyama, 2002; Wong, 2003).

RADIATION ONCOLOGY PRACTICE

Background of Fractionated Radiation Therapy

STANDARD FRACTIONATION

In the early 20th century, controversy grew concerning two different approaches for radiation therapy delivery in the treatment of human cancers. One school recommended the delivery of a massive radiation dose within a short time interval. The assumption was that a rapidly growing tumor would retain the capacity to recover quickly from radiation damage if a tumoricidal dose was not given in the first treatment session (Thames, 1992). Alternatively, smaller doses given over many days to weeks were advocated by others as a method to minimize radiation side effects.

The controversy was resolved when Coutard (1932), along with the work of others, found success with this type of *fractionated IR* . As a result, in the U.S. since the 1950s, the practice of giving 1.8 to 2 Gy a day, 5 days a week has been considered standard or conventional.

ALTERED FRACTIONATION

In an effort to increase local tumor control as well as decrease long-term complications, fraction size and overall treatment time duration have been manipulated, leading to a variety of altered fractionations. Two major strategies have been employed: hyperfractionation and accelerated treatment. These both differ from the standard therapy in that multiple fractions are given each day.

With hyperfractionation, the reduction of late damage to normal tissues is sought, and accordingly, a smaller dose per fraction is given. Two or more fractions are administered each day.

As noted earlier, there is tumor repopulation during a conventional 6- to 7-week course, which may lead to treatment failure. To counter these problems, an accelerated treatment schedule may be used. This entails shortening the treatment duration with or without a decrease in total dose. The usual weekend break is either shortened or eliminated. With accelerated treatment, however, severe acute reactions are frequently encountered. Often a mandatory rest period in the middle of the treatment course is required (Wang, 1988).

Altered fractionation has been studied in cervical cancer. The tumor control, late toxicity, and survival results were similar to historical rates achieved by standard fractionation (Grigsby, 2002; Komaki, 1994). However, it was poorly tolerated, especially when large-field radiation therapy and chemotherapy or both were added (Grigsby, 1998; Marcial, 1995).

Tumor Control Probability

With most of epithelial cancers, the probability of IR to control a cancerous mass depends on the tumor size and intrinsic radiosensitivity and on the radiation dose and delivery schedule. For example, within a given stage, large tumors are more difficult to control with IR than smaller ones (Bentzen, 1996; Dubben, 1998).

INTRINSIC RADIOSENSITIVITY

Although it is recognized that a tumor's radiosensitivity in general is determined by its pathologic type, even cancers within a similar histology may have variable responses to IR (Table 28-3). In addition, heterogeneity within a given tumor may explain this varied response. Another factor that seems to play a role in determining tumor radiosensitivity is its ability to repair radiation damage. For example, the rate of DNA double-strand break repair was found to correlate well with radiosensitivity of tumors (Schwartz, 1988, 1996; Weichselbaum, 1992).

Table 28-3 Radiosensitivity of Some Selected Cancers

Sensitivity	Cancer Type
Highly sensitive	Lymphoma, dysgerminoma, small cell cancer, embryonal cancer
Moderately sensitive	Squamous carcinoma, adenocarcinoma
Poorly sensitive	Osteosarcoma, glioma, melanoma

TREATMENT TIME

When protracted time intervals are required to complete a fractionated IR course, tumor control probability decreases, especially in rapidly proliferating epithelial cancers. Therefore, treatment breaks or delays for any reason should be minimized. In a retrospective review of 209 patients with stage 1 to 3 cervical cancer treated with IR, the 5-year pelvic control and overall survival rates were better for those who completed the treatment in less than 55 days (87 percent and 65 percent, respectively) than for those who did so in more than 55 days (72 percent and 54 percent, respectively) (Petereit, 1995).

Tumor Hypoxia

With primary radiation therapy, tumor hypoxia is one of the major factors leading to poor local tumor control and poor survival in patients with cervical cancer (Brizel, 1999; Nordsmark, 1996). For example, the close relationship between tumor hypoxia, anemia, and angiogenesis was demonstrated in a study involving 87 patients with stage 2, 3, and 4 cervical cancer treated with IR only. Of these, patients with a hemoglobin level of less than 11 g/dL, a median tumor oxygen tension less than 15 mm Hg, and an

increased tumor microvascular density had decreased 3-year survival (Dunst, 2003). For this reason, many strategies have been devised to overcome tumor hypoxia.

HYPERBARIC OXYGEN

Hyberbaric oxygen used in conjunction with radiation therapy in stage 2 and 3 cervical cancer has not been shown to be effective in clinical studies (Dische, 1999). In addition, there is concern that hyberbaric oxygen may accelerate tumor growth (Bradfield, 1996).

A more convenient method of increasing the delivery of oxygen to tissues involves manipulating blood vessel hemodynamics with either carbogen or nicotinamide. *Carbogen* (95-percent oxygen and 5-percent carbon dioxide) is an oxygen preparation with increased intratumoral diffusion capabilities. When inhaled during concurrent external radiation therapy, carbogen has been shown to increase tumor oxygen pressure and is well tolerated (Aquino-Parsons, 1999). Alternatively, *nicotinamide* is the amide derivative of vitamin B_3 and has been shown to prevent intermittent vascular shutdown. In combination, carbogen and nicotinamide are thought to increase oxygen delivery to diffusion-limited hypoxic regions.

BIOREDUCTIVE AGENTS

This family of hypoxic sensitizers exploits the tumor's hypoxic environment to initiate a series of hypoxia-activated biochemical events. These steps lead to the production of cytotoxic agents that selectively kill hypoxic cells. During the last decades, the agents mitomycin C and tirapazamine, have been proved clinically effective (Craighead, 2000; Nguyen, 1991; Rischin, 2001).

BLOOD TRANSFUSION

In clinical practice, it is desirable to bring the hemoglobin level of patients receiving IR to at least 12 g/dL. It has long been believed that transfusion ameliorates tumor hypoxia and increases IR response. For example, in a review of a group of 204 women with cervical cancer who were treated with IR, 26 percent had a hemoglobin level of <11 g/dL, either before or during the IR course. They received packed red blood cell transfusion. Of these, only 18 percent of the women who received transfusions were able to maintain a hemoglobin level of >11 g/dL throughout the treatment. This subset of women had a similar 5-year disease-free survival rate of 71 percent compared with a group of women who never required transfusion. The disease-free survival rate was only 26 percent for those with persistent anemia. Not all patients, however, showed marked benefit from transfusion, especially those with nodal metastasis, late stage, and large tumor size (Kapp, 2002).

RECOMBINANT HUMAN ERYTHROPOIETIN

In addition to transfusion, recombinant human erythropoietin (EPO) has been used to correct anemia and is discussed in Chapter 27, Growth Factors. Clinically however, this therapy has not proved to be beneficial in those receiving RT. In a Southwest Oncology Group phase II multi-institutional trial, EPO and iron supplements produced an inadequate increase in hemoglobin levels, There was additional concern that EPO increased the risk of deep vein thrombosis (Lavey, 2004; Wun, 2003). Moreover, according to one report, it was more economical to administer blood transfusions than EPO to correct anemia in patients with cervical cancer who were receiving concurrent cisplatin and IR (Kavanagh, 2001).

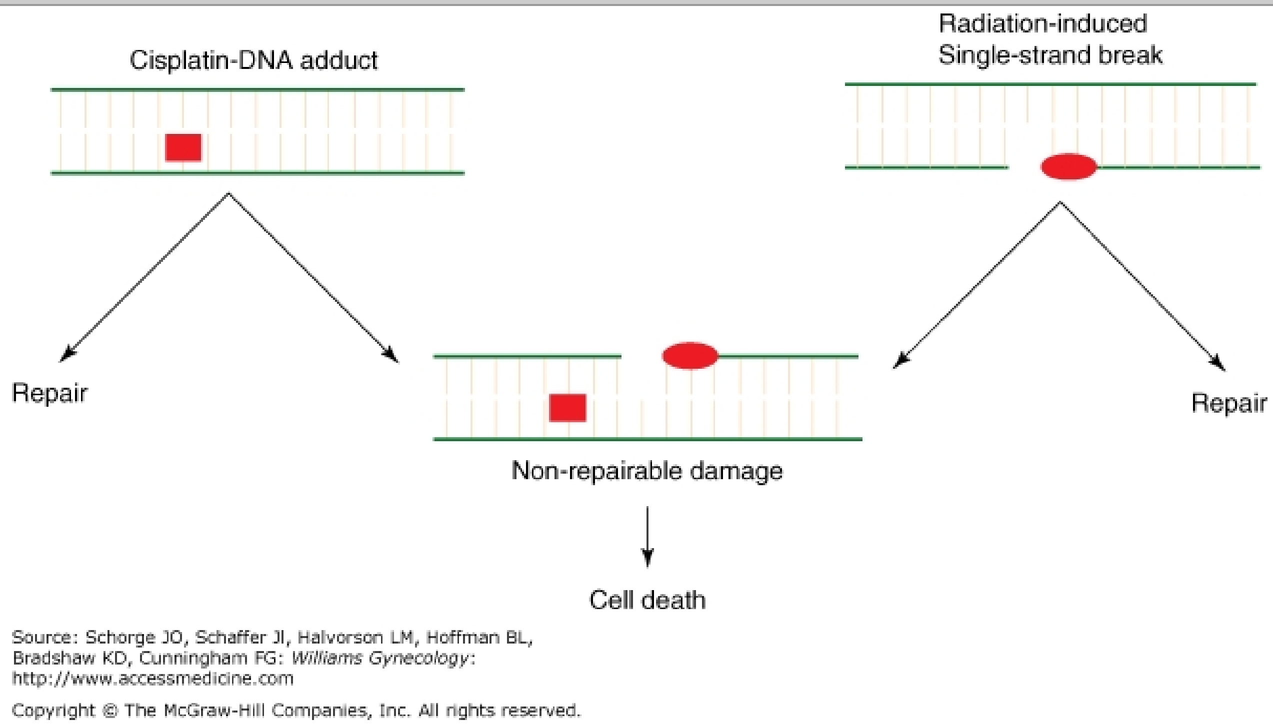
Combination of Ionizing Radiation and Chemotherapy

Ionizing radiation as a single modality rarely controls locally advanced gynecologic cancers. Various factors such as tumor hypoxia, high probability of distant metastasis, and inability of pelvic tissues to tolerate high IR doses are purported causes. For many decades, IR has been combined with chemotherapy or surgery to increase local disease control and decrease distant metastasis. Ionizing radiation and chemotherapy can be administered in a concurrent or alternating fashion. When adding this modality to IR, however, efforts to maximize tumoricidal effects while minimizing overlapping toxicities should be a priority (Steel, 1979). Platinum compounds are most commonly used with IR in the management of gynecologic cancers.

PLATINUM COMPOUNDS

Both IR and cisplatin have DNA as targets causing SSB, DSB, and base damage. Although most lesions are repaired, if a cisplatin-induced adduct is in close proximity with an IR-induced SSB, the damage is irreparable and leads to cell death (Fig. 28-11) (Amorino, 1999; Begg, 1990). In addition, irradiated cell membranes may be more permeable to carboplatin, allowing an increased cellular uptake of the drug (Yang, 1995).

FIGURE 28-11



Model showing response to DNA damage. A cisplatin DNA adduct or a radiation-induced single-strand break is likely repairable. When both occur in close proximity, however, irreparable damage may lead to cell death. *(From Hennequin, 2002, with permission.)*

NUCLEOSIDE ANALOGS

Agents such as fludarabine and gemcitabine inhibit DNA synthesis and metabolism. Cells at the G_1 /S junction of the cycle are involved in DNA synthesis and therefore are blocked from progressing. The remaining cell population, however, is synchronized at the G_2 /M junction and is sensitive to IR. Gregoire and associates (1994, 1999) found that radiation was most effective when IR was delivered 24 to 72 hours after nucleoside analog administration.

TAXANES

The taxanes such as paclitaxel and docetaxel dysregulate microtubule function and block cells at the G_2 /M junction when cells are most sensitive to IR (Mason, 1999).

Combination of Ionizing Radiation and Surgery

Ionizing radiation can be given before, after, or at the time of surgery. With this combination, surgical resection and its associated morbidity can often be minimized yet still achieve tumor control. For example, the combination of IR and surgery in locally advanced vulvovaginal cancer can allow surgeons to avoid extensive surgery, such as pelvic exenteration (Boronow, 1982). Typically, whenever IR is indicated with surgery, some form of chemotherapy is also added in an adjuvant fashion.

PREOPERATIVE RADIATION THERAPY

Primary cancers tend to locally infiltrate surrounding normal tissues with microscopic extension. For this reason, IR can be delivered prior to surgery to decrease the potential of locoregional and distant tumor dissemination as well as the likelihood of positive surgical margins. To sterilize those areas of subclinical infiltration, doses of 40 to 50 Gy given during 4 to 5 weeks are required. Although preoperative RT is not expected to render the main tumor mass cancer-free at the time of surgery, it is common to find no evidence of cancer in the surgical specimen. In patients who presented with unresectable cancers, preoperative RT can transform them into suitable candidates for a surgical attempt (Montana, 2000).

Despite these advantages, administering preoperative RT may unnecessarily expose patients to IR because the true pathologic tumor staging is unknown. Moreover, if the nodal status is normal at the time of surgery, the clinician is faced with the question of whether there initially were lymph nodes containing tumor that were sterilized by the preoperative regimen. This is important, as patients with initially positive lymph nodes tend to develop distant metastasis and typically would require further treatment. Another problem encountered is the management of those patients with pathologically proven residual cancer within the irradiated areas. The pathologist may not be able to adequately ascertain the viability of those residual cells, especially when surgery is performed soon after IR. Therefore, surgery is usually delayed 4 to 6 weeks after completion of IR. By then, the acute reactions from IR have subsided, and pathologic interpretation of the resected specimen is easier.

POSTOPERATIVE RADIATION THERAPY

Often following surgery, a high probability for local recurrence may be predicted by factors such as positive margins, lymph node metastases, lymphovascular invasion, and high-grade cancer. In these cases, postoperative RT may be advantageous and is ideally delivered 3 to 6 weeks following surgery to allow initial wound healing (Sedis, 1999). Because the pathologic stage is known, management can be individualized and unnecessary RT avoided (Rushdan, 2004). The RT fields should encompass the operative bed due to the possibility of tumor contamination at the time of surgery.

INTRAOPERATIVE RADIATION THERAPY

Infrequently, IR can be delivered during surgery by either interstitial brachytherapy or by an electron beam produced by a dedicated linear accelerator installed in the operating room. This technique is indicated in selected patients with recurrent gynecologic cancers. A single dose of 10 to 20 Gy is typically delivered to the area at risk for recurrence or suspected of harboring residual cancer (Gemignani, 2001; Yap, 2005).

Normal Tissue Response to Ionizing Radiation

In general, radiation therapy is less well tolerated when: (1) the volume of tissues irradiated is large; (2) the IR dose is high; (3) the dose per fraction is large; and (4) the patient's age is advanced. Furthermore, a number of other factors can exacerbate the radiation damage to normal tissues. These include previous surgery, concurrent chemotherapy, infection, diabetes mellitus, hypertension, and inflammatory conditions, for example Crohn disease and regional enteritis.

When tissues with a rapid proliferation rate such as epithelium of the small intestine or oral cavity are irradiated, the onset of acute clinical signs and symptoms develop within a few days to weeks. This contrasts with tissues such as muscular, renal, and neural tissues, which have low proliferation rates and may not display signs of radiation damage for months to years after treatment. The concept of tolerance doses for normal tissues was developed as a guide to avoid serious complications in clinical radiation oncology practice.

EPITHELIUM AND PARENCHYMA

Atrophy is the most consistent sequela of radiation therapy and affects all lining epitheliaâ€”including skin and the epithelia of the gastrointestinal, respiratory, and genitourinary tracts and the endocrine glands. Additionally, necrosis and ulceration may develop. The capillary is the most sensitive vessel to IR damage, and ischemia results from damage to the endothelium, rupture of capillary walls, loss of capillary segments, and reduction of microvascular networks. Moreover, in large arteries, atheroma-like calcifications develop (Friedlander, 2003; Zidar, 1997). Histologic changes of the epithelium may also develop, and atypical and dysplastic transformations are the most frequent.

In addition to epithelial changes, fibrosis within the submucosa and deep soft tissues frequently follows IR. This clinically leads to tissue contracture and stenosis (Fajardo, 2005).

SKIN

Four general types of skin reactions may follow radiation therapy. In order of severity, they include erythema, dry desquamation, moist desquamation, and skin necrosis. For many women during a 6- to 7-week IR course, these reactions are common, with the exception of necrosis. Within 1 week following IR, the skin first develops mild erythema. By the third week, redness becomes more pronounced and dry desquamation begins. After 5 to 6 weeks, moist desquamation ensues with epidermal sloughing, followed by

serum and blood oozing through the denuded skin. This reaction is most pronounced in concealed areas of the body, such as the inguinal, axillary, and inframammary regions.

Preventively, throughout and after an IR course, the skin should be kept clean and aerated. For dry desquamative findings, ointments (Aquaphor, Beiersdorf, Hamburg, Germany) or aloe veraâ€"containing creams promote dermal hydration with an emollient effect. In the moist desquamation phase, hydrogen peroxide and water can be used for wound cleaning. Additional skin treatment may include moisturizers (Biafine, Johnson and Johnson, New Brunswick, NJ), whirlpool sessions, sitz baths, and silver sulfadiazineâ€"containing, nonadhering dressings (Vigilon, Bard Medical, Covington, GA) for weeping areas. Importantly, individuals should avoid applying heat pads, soaps, or alcohol-based lotions to irradiated skin.

Regeneration of the epithelium starts soon after IR treatment and is usually complete in 4 to 6 weeks. Months after IR, areas of skin hyper- and hypopigmentation can be seen. The skin remains atrophied, thin, and dry.

VAGINA

Radiation therapy directed to the pelvis commonly leads to acute vaginal mucositis. Although mucosal ulceration is rare, discharge is present in most cases. For these women, a dilute hydrogen peroxide and water solution may provide symptomatic relief. In contrast to acute changes, delayed reactions to IR may include vaginal shortening, atrophic vaginitis, and formation of synechiae or telangiectasia. Preventively, these complications may be avoided if women are instructed regarding the use of dilators or if vaginal intercourse is resumed following treatment. Lastly, rectovaginal or vesicovaginal fistulas can develop after IR, especially in advanced-stage cancers (see Chap. 26, Other Causes).

For those women who remain sexually active following radiation therapy, water-based lubricants (Astroglide, Biofilm, Vista, CA and K-Y Jelly (Johnson and Johnson, New Brunswick, NJ) may be of benefit during intercourse. Unlike lubricants, which have no sustained effects, vaginal moisturizers form a lubricated coating on the vaginal epithelium and retain moisture for 48 to 72 hours. For this reason, vaginal moisturizers (Replens, Lil' Drug Store Products, Cedar Rapids, IA and K-Y Silk-E, Johnson and Johnson, New Brunswick, NJ) can be used regularly at other times to maintain lubricated vaginal tissues. Alternatively, topical estrogen cream may be used to improve atrophic symptoms (see Table 22-7).

Although these products may improve the vaginal changes following radiation treatment, persistent adverse vaginal changes and sexual dysfunction during the 2 years after IR have been documented in a longitudinal study of 118 women who completed radiation therapy for cervical cancer. However, 63 percent of those who engaged in sexual activities before IR therapy continued to do so following treatment, although with less frequency (Jensen, 2003).

OVARY AND PREGNANCY OUTCOMES

The effects of IR on ovarian function depend on the IR dose and patient age. For example, a dose of 4 Gy may cause sterility in 30 percent of young women, but in 100 percent of those older than 40 years. In addition, fractionated IR seems to be more damaging to the ovaries. Ash and colleagues (1980) noted that after 10 Gy given in 1 fraction, 27 percent of women recovered ovarian function compared with only 10 percent of those receiving 12 Gy in 6 days. In patients with gynecologic cancers who receive pelvic IR, symptoms of ovarian failure mirror those of natural menopause and treatment of symptoms is similar (see Chap. 22, Symptoms of Menopause).

To minimize radiation exposure to the ovaries of premenopausal women, these organs may be surgically repositioned, termed *transposition,* out of the radiation field. Despite this maneuver, several investigators have reported high rates of ovarian failure when the ovarian dose was more than 3 to 5 Gy. In addition, a birth incidence of only 19 percent was reported among the patients who could conceive (Chambers, 1991; Haie-Meder, 1993). Among female childhood-cancer survivors who received abdominal irradiation, higher spontaneous abortion rates and lower first-born birth weights were observed compared with cancer survivors who were not irradiated (Hawkins, 1989).

BLADDER

Most patients receiving IR to the pelvis note some symptoms of acute cystitis within 2 to 3 weeks of beginning treatment. Although urinary frequency, spasm, and pain develop commonly, hematuria is rare. Typically, flavoxate hydrochloride (Urispas), oxybutynin (Ditropan), phenazopyridine hydrochloride (Pyridium, Warner Chilcott, Rockaway, NJ) or fluids ad lib promptly relieves symptoms.

Antibiotics may be used when indicated.

Major chronic complications following radiation therapy are infrequent and include bladder contracture and hematuria. For severe hematuria, bladder saline irrigation, transurethral cystoscopic fulguration, and temporary urinary diversion are proven techniques. Hyperbaric oxygen therapy has also been described.

SMALL BOWEL

The small bowel is particularly vulnerable to IR acute early damage. For example, after a single dose of 5 to 10 Gy, the crypt cells are destroyed. The villi become denuded and an ensuing acute malabsorption syndrome causing nausea, diarrhea, vomiting, and crampy pain follows. Antinausea and antidiarrhea medications may be added to general instructions of adequate fluid intake and a low-lactose, low-fat, and low-fiber diet (see Tables 39-13 and 25-5). Additionally, bowel antispasmodics with sedatives (Donnatal, PBM Pharmaceuticals, Gordonsville, VA) are particularly helpful.

Patients should be warned about the late, chronic nature of radiation-induced enteritis. With this, intermittent diarrhea, crampy abdominal pain, nausea and vomiting, which in combination may mimic a low-grade bowel obstruction, are frequent. Those patients with co-morbidities, such as obesity, small vessel diseases resulting from diabetes or hypertension, previous abdominal surgeries, and inflammatory conditions of the pelvis or bowel, are at increased risk.

Preventively, several types of devices have been surgically inserted to displace the small bowel from the pelvis. These have included saline-filled tissue expanders, omental slings, and absorbable mesh (Hoffman, 1998; Martin, 2005; Soper, 1988). Furthermore, defining the areas at risk with surgical clips and careful radiation therapy planning, including the use of IMRT may minimize bowel toxicity (Portelance, 2001). More recent advances include the intravenous use of radiation protectors such as amifostine (Athanassiou, 2003). Amifostine is thought to attenuate radiation cell injury through its ability to reduce levels of radiation-induced free radicals.

RECTOSIGMOID

Commonly, within a few weeks after IR initiation, patients may develop diarrhea, tenesmus, and mucoid discharge, which can be bloody. In these cases, antidiarrheal medications, a low-residue diet, steroid retention enema, and hydration are the mainstays of management. Alternatively, rectal bleeding may be seen months to years after IR treatment. Hemorrhage may at times be severe and require blood transfusion. Moreover, invasive procedures may be needed to control bleeding neovasculature. Steps may include topical application of 4-percent formalin, cryotherapy, and vessel coagulation with laser (Kantsevoy, 2003; Konishi, 2005; Smith, 2001; Ventrucci, 2001). During the evaluation of late-onset rectal bleeding, barium enema is often indicated. The study usually reveals narrowing of the rectosigmoid lumen and wall thickening. In case of severe obstruction, resection of the involved colonic segment is necessary. In addition, rectovaginal fistulas may result from RT (see Chap. 25, Rectovaginal Fistula). Small fistulas may heal over many months following a diverting colostomy.

KIDNEY

Manifestations of acute radiation nephropathy typically appear 6 to 12 months after IR exposure. The patients develop hypertension, edema, anemia, microscopic hematuria, proteinuria, and decreased creatinine clearance (Luxton, 1964). Although deteriorating renal function is occasionally reversible, it usually worsens and leads to chronic nephropathy. Patients receiving concurrent chemotherapy and IR require special consideration, because of the nephrotoxicity associated with many chemotherapy agents (see Chap. 27).

Radiation-Induced Carcinogenesis

Development of a secondary, radiation-induced cancer depends on the age at exposure, dose of IR, and susceptibility of specific tissue types to radiation-induced carcinogenesis (Table 28-4). The accepted criteria for the diagnosis of IR-induced cancer require that the cancer be located within the previously irradiated regions and that its pathology differs from that of the original malignancy. Additionally, there should be a latent period of at least a few years.

Table 28-4 Susceptibility of Selected Tissues to Radiation-Induced Cancer	
Susceptibility	**Tissues**
High	Bone marrow, female breast, thyroid
Moderate	Bladder, colon, stomach, liver, ovary
Low	Bone, connective tissue, muscle, cervix, uterus, rectum

Adapted from Mettler, 1995, with permission.

In general, those receiving higher IR doses and those exposed at an earlier age have increased risks for second malignancies. Secondary tumor development latency also varies depending on the type of second malignancy. For example, the latent period before IR exposure and the clinical appearance of leukemia is less than 10 years, whereas solid tumors may not develop for decades. Of note, for most radiation-induced malignancies, the clinical appearance of these cancers does not appear until the age when non-irradiated patients would spontaneously develop that particular cancer type. Moreover, radiation-induced and spontaneously developing cancer cells have identical pathologic characteristics. The most common example is development of uterine sarcoma years after pelvic radiation for treatment of cervical cancer (Mark, 1996).

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PREINVASIVE LESIONS OF THE LOWER GENITAL TRACT: INTRODUCTION

Since the introduction of the Papanicolaou (Pap) test in the 1950s, cervical cytology screening has been associated with a significant reduction in the incidence of and mortality from invasive squamous cervical cancer (Saslow, 2002). Annually, approximately 7 percent of U.S. women who undergo this screening will have abnormal cytologic results requiring a clinical response (Jones, 2000). Accordingly, office gynecology frequently involves the diagnosis and management of lower genital tract (LGT) preinvasive disease.

DISEASE SPECTRUM OF LOWER GENITAL TRACT NEOPLASIA

The term *intraepithelial neoplasia* refers to squamous epithelial lesions of the lower genital tract, which are considered to be cancer precursors, but lack features of invasive cancer. Lesions are diagnosed by biopsy and subsequent histologic evaluation. Cervical, vaginal, vulvar, and perianal intraepithelial neoplasia (CIN, VaIN, VIN, and AIN) demonstrate a disease spectrum ranging from mildly dysplastic cytoplasmic and nuclear changes to those of severe dysplasia. With these changes, there is no invasion through the basement membrane, which defines invasive cancer.

The severity of a lesion is graded according to the proportion of epithelium affected from the basement membrane upwards. In the case of CIN, abnormal cells confined to the lower third of the squamous epithelium are referred to as *mild dysplasia* or *CIN 1;* extending into the middle third as *moderate dysplasia* or *CIN 2;* and into the upper third as *severe dysplasia* or *CIN 3,* with full-thickness involvement called *carcinoma in situ* (CIS). Even though lesions of the vulva and vagina are graded in like fashion, there are recent important changes in terminology regarding the description of vulvar squamous lesions with premalignant potential (New Modified Terminology).

In contrast, being only one cell layer thick, the cervical columnar epithelium does not demonstrate an analogous neoplastic disease spectrum. Histologic abnormalities are therefore limited to *adenocarcinoma in situ* (AIS) or *adenocarcinoma.*

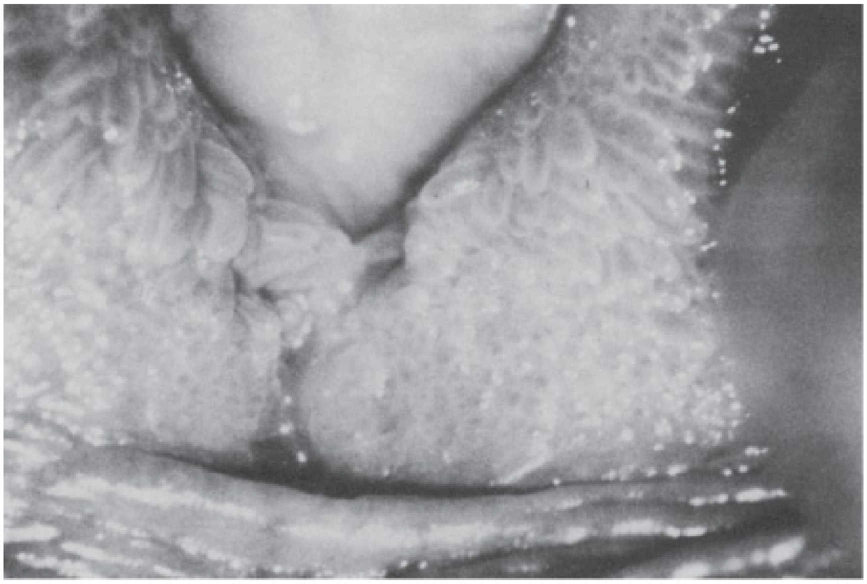
Since the introduction of new cervical cytology terminology in 1988, the term *squamous intraepithelial lesion* (SIL) has become synonymous with intraepithelial neoplasia. Because histologic changes of human papillomavirus (HPV) infection and CIN 1 are similar and cannot be distinguished reliably, they are termed *low-grade squamous intraepithelial lesions* (LSILs), whereas CIN 2 and 3 may be designated as *high-grade SIL* (HSIL) (Saslow, 2002).

ANATOMIC CONSIDERATIONS

External Genitalia

Precancerous lesions of the female LGT are often multifocal, can involve any of its structures, and may appear similar to benign processes. For example, minute epithelial projections, termed *micropapillomatosis labialis,* may be present on the inner labia minora's epithelial surface (Fig. 29-1). Each papillary projection arises from its own individual base. These can be mistaken for HPV-related lesions, which in contrast, tend to be multifocal, asymmetric, and have multiple papillations arising from a single base (Dexeus, 2002; Ferris, 2004). Micropapillomatosis often shows spontaneous regression and treatment is unnecessary (Bergeron, 1990).

FIGURE 29-1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Micropapillomatosis labialis is a normal variant of vulvar anatomy encountered along the posterior, inner aspects of the labia minora and lower vagina. In contrast to condylomatous change, projections are uniform in size and shape and arise singly from their base attachments. *(From Bergeron, 1990, with permission.)*

Vagina

The vagina is lined by nonkeratinized squamous epithelium and glands are absent. However, areas of columnar epithelium can occasionally be found within the vaginal squamous mucosa, a condition termed *adenosis.* It is most commonly attributable to in utero exposure to exogenous estrogen during fetal development, particularly diethylstilbestrol (DES) (see Chap. 18, Acquired Uterine Defects) (Trimble, 2001). Careful palpation of the vagina is warranted, as clear cell adenocarcinoma, also associated with DES, may be palpable before it is visible.

Cervix

SQUAMOUS AND COLUMNAR EPITHELIA

Colposcopically, the squamous epithelium of the cervix appears as a featureless, smooth, pale pink surface. Blood vessels lie below this layer and therefore are not visible or are seen only as a fine capillary network. The mucin-secreting columnar epithelium of the endocervix appears red and velvety due to the proximity of blood vessels beneath the one-cell-layer-thick epithelium. The columnar epithelium is characterized by infoldings or clefts and is commonly referred to as "glandular". This is technically incorrect, as true glands, consisting of acini and ducts, are not present (Ulfelder, 1976). Nonetheless, "glandular" abnormalities are reported in the Bethesda nomenclature for cervical cytology (Kurman, 1994).

SQUAMOCOLUMNAR JUNCTION

During embryogenesis, upward migration of stratified squamous epithelium from the urogenital sinus and vaginal plate is thought to replace mÃ¼llerian epithelium (see Chap. 18, Ductal System Development) (Ulfelder, 1976). This process usually ends at the external cervical os, forming the original squamocolumnar junction (SCJ). In a minority, such as those with in utero DES exposure, this migration is incomplete, leading to location of the SCJ in the upper vagina (Kaufman, 2005).

The location of the SCJ varies with age and hormonal status (Fig. 29-2). It everts outward onto the ectocervix during adolescence, pregnancy, and with use of combination hormonal contraceptives. It regresses into the endocervical canal with menopause and

other low-estrogen states such as prolonged lactation and use of progestin-only contraceptives (Anderson, 1991).

FIGURE 29-2

A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

The location of the squamocolumnar junction (SCJ) is variable. **A.** The SCJ is located on the ectocervix and is fully visualized. **B.** The SCJ is located near the external os and is not entirely visible.

The rise in estrogen at puberty leads to glycogenation of the nonkeratinized squamous epithelium of the LGT. Glycogen provides a carbohydrate source for lactobacilli, which dominate the normal vaginal flora in reproductive-aged women (see Chap. 3). The lactobacilli produce lactic acid, lowering the vaginal pH to less than 4.5. The exposure of the columnar epithelium to this low pH stimulates squamous metaplasia, the conversion of one type of normal epithelium (columnar) into another (squamous).

Squamous metaplasia is a normal process and occurs most actively immediately adjacent to the original SCJ, creating a zone of metaplastic epithelium termed the *transformation zone* (TZ), between the original SCJ and the columnar epithelium.

TRANSFORMATION ZONE AND CERVICAL NEOPLASIA

Nearly all cervical neoplasia, both squamous and columnar, develops within the transformation zone, usually adjacent to the new SCJ (Anderson, 1991). Theoretically, cervical cells undergoing metaplasia are particularly vulnerable to the oncogenic effects of HPV and co-carcinogens. Metaplasia is most active during adolescence and pregnancy. This may explain why early age of sexual activity and first pregnancy are known risk factors for cervical cancer.

HUMAN PAPILLOMAVIRUS

The role of this virus in the genesis of essentially all cervical neoplasia and a significant portion of vulvar, vaginal, and anal neoplasia is firmly established.

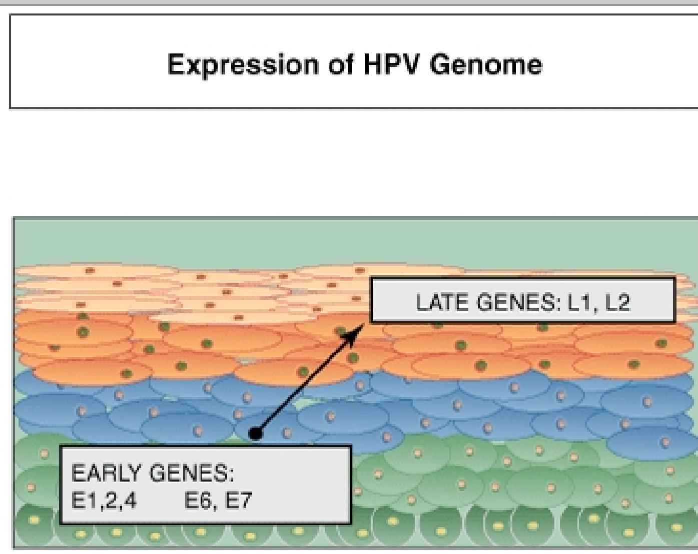
Basic Virology

Human papillomavirus is a nonenveloped DNA virus with a protein capsid. It infects epithelial cells exclusively and approximately 30 to 40 HPV types have an affinity for infecting the lower anogenital tract.

VIRAL LIFE CYCLE

The circular, double-stranded HPV genome consists of only nine identified open reading frames (ORF) (Southern, 1998). The "early" (E) genes govern functions early in the viral life cycle such as DNA maintenance, replication, and transcription. The "late" (L) genes encode capsid proteins needed late in the viral life cycle to complete assembly into new, infectious viral particles (Beutner, 1997; de Villiers, 2004). Completion of the viral life cycle takes place only within an intact squamous epithelium. Early genes are expressed in the lower layers and late genes are expressed in the more superficial layers, in synchrony with epithelial differentiation. Viral replication is completed within the most superficial epithelial layers. HPV is a nonlytic virus, and therefore infectiousness depends upon desquamation of infected cells (Fig. 29-3) (Doorbar, 2005).

FIGURE 29-3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

The human papillomavirus life cycle is completed in synchrony with squamous epithelium differentiation. Early genes, including the *E6* and *E7* oncogenes, are expressed most strongly within the basal and parabasal layers. The late genes encoding capsid proteins are expressed later in the superficial layers. Intact virus is shed within superficial squama. Late genes are not strongly expressed in high-grade neoplastic lesions.

VIRAL TYPES

More than 100 HPV types have now been identified. Clinically, HPV types are classified as high-risk (HR) or low-risk (LR) based upon their cervical cancer oncogenicity. Low-risk HPV types 6 and 11 cause nearly all genital warts and a minority of subclinical HPV infections. Low-risk HPV infections are rarely, if ever, oncogenic.

In contrast, the HR HPV types include 16, 18, 31, 33, 35, 45, and 58 and account for approximately 95 percent of cervical cancer cases worldwide. Other HR HPV types less often associated with neoplasia include 39, 51, 52, 56, 59, 68, 73, and 82 (Bosch, 2002; Lorincz, 1992; Munoz, 2003).

The most common HR HPV types (16, 18, 45, and 31) found in cervical cancer are also the most prevalent in the general population. Specifically, HPV 16 is the dominant cancer-related HPV, accounting for 40 to 70 percent of invasive squamous cell cervical cancers worldwide (Bosch, 2002; Munoz, 2003). This serotype is also the most common HPV found among low-grade lesions and in women without neoplasia (Herrero, 2000).

Like HPV 16, viral types 18, 45, and 56 are also highly oncogenic (Lorincz, 1992). The prevalence of HPV 18 is much lower than that of HPV 16 in the general population, but it is found in up to 25 percent of squamous cell carcinomas, and in an even higher proportion of cervical adenocarcinomas and adenosquamous carcinomas (Ferris, 2004).

Additionally, HPV 18 is thought to play a dominant role in the development of rapid transit cervical cancers, that is, those that appear to develop without the prolonged premalignant phase typical of most cervical cancers. These cancers develop within 1 to 3 years of negative cervical cytology, are more likely to be adeno- or adenosquamous, and develop in younger women (Hildesheim, 1999; Lorincz, 1992; Schwartz, 1996). However, the existence of rapid transit lesions remains controversial, as these may actually reflect late-detected endocervical disease, which is more likely to be missed by cytologic screening (Schwartz, 1996).

Transmission

Transmission of genital HPV usually requires sexual contact with the genital skin, mucous membranes, or body fluids of a partner with either warts or subclinical infection (Abu, 2005; American College of Obstetricians and Gynecologists, 2005b). Exceptions are considered to be extremely rare.

Little is known about the infectivity of subclinical HPV, but it is assumed to be high, especially in the presence of high viral counts. Through microabrasion of the genital epithelium during sexual contact, HPV likely gains access to the basal cell layer. Once infected, the basal cells become a viral reservoir.

Genital HPV infection is multifocal, involving more than one lower reproductive tract site in most cases (Bauer, 1991; Campion, 1991; Spitzer, 1989). Therefore, neoplasia at one genital site increases risk of neoplasia elsewhere within the lower genital tract.

MODES OF TRANSMISSION

High-risk HPV cervical infection is not seen in women who have not experienced penetrative sexual contact, although they may occasionally test positive for non-oncogenic or low-risk types at the vulva or vagina, perhaps due to vaginal tampon use or digital penetration (Andersson-Ellstrom, 1996; Fairley, 1992; Ley, 1991; Rylander, 1994; Winer, 2003).

Oral-genital and hand-genital transmissions are possible, but appear to be far less common than with genital-genital, particularly penile-vaginal penetrative contact (Winer, 2003). Nonsexual transmission of genital HPV types is theoretically possible, but is probably rare in sexually active adults. Fomite transmission, known to occur with nongenital warts, is unproven (Ferenczy, 1989).

Women who have sex with women frequently report past sexual experiences with men. This subgroup of women have rates of HR-HPV positivity, abnormal cervical cytology, and high-grade cervical neoplasia similar to those of heterosexual women, but undergo cervical cancer screening less often (Marrazzo, 2000). Those who have never had sex with men appear to be at similar risk, implying that digital, oral, and object contact place them at risk of HPV infection. Therefore, women who are sexually active should undergo cervical cancer screening according to current recommendations regardless of sexual orientation.

CONGENITAL INFECTION

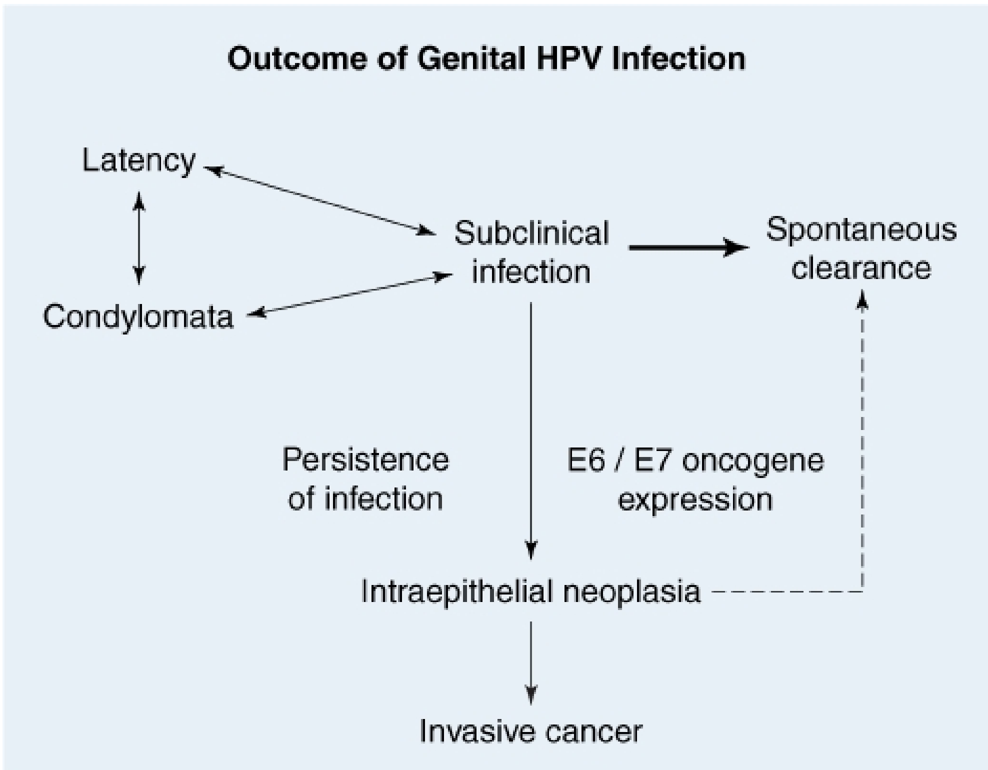
Congenital HPV infection by vertical infection from mother to infant develops rarely. Conjunctival, laryngeal, vulvar, or perianal warts present at birth or that develop within 1 to 3 years of birth are most likely due to perinatal exposure to maternal HPV in the absence of sexual abuse (Cohen, 1990). Infection is not related to the presence of maternal genital warts or route of delivery (Silverberg, 2003; Syrjanen, 2005). Accordingly, cesarean delivery is recommended for HPV-related infection only in cases of large genital warts that would likely obstruct delivery or avulse with cervical dilation.

Genital warts that develop in children after infancy are always cause to seriously consider sexual abuse. However, infection by nonsexual contact, autoinoculation, or fomite transfer is also possible, as evidenced by the finding of nongenital HPV types in a significant minority of cases (Cohen, 1990; Obalek, 1990; Siegfried, 1997).

Outcome of HPV Infection

Genital HPV infection results in a variety of outcomes (Fig. 29-4). Infection may be *latent* or *expressed.* Expression is either *productive,* with formation of new virus, or *neoplastic,* causing preinvasive disease or malignancy. Most productive and neoplastic infections are subclinical, rather than clinically apparent, as with genital warts or obvious malignancy. Finally, HPV infection can be *transient* or *persistent.* Neoplasia is the least common outcome of genital HPV infection.

FIGURE 29-4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

The natural history of genital HPV infection is variable between individuals and over time. Subclinical infection and spontaneous resolution of apparent infection are the most common outcomes. Neoplasia is the least common manifestation, usually developing over years as the result of persistent infection.

LATENT INFECTION

Latent infection refers to that in which cells are infected, but HPV remains quiescent. There are no tissue effects, as the virus is not reproducing. Little is known about the incidence, natural history, or significance of latent HPV infection, as the virus is present below detectable levels.

EXPRESSED PRODUCTIVE INFECTION

Productive infections have little or no malignant potential because eventual host cell death is required to complete the viral life cycle. The intact, circular HPV genome remains unintegrated into the infected cell's chromosomes and its oncogenes are expressed at only very low levels (Durst, 1985; Stoler, 1996).

In both the female and male genital tracts, productive HPV infections produce either visible genital warts, called *condylomata acuminata,* (see Chap. 3, External Genital Warts) or much more commonly, subclinical infections known as low-grade squamous intraepithelial lesions (LSILs).

EXPRESSED NEOPLASTIC INFECTION

In cancerous lesions, the circular HPV genome integrates linearly at random locations into a host chromosome and unrestrained transcription of the E6 and E7 oncogenes follows (Durst, 1985; Stoler, 1996). Their products, the E6 and E7 oncoproteins, interfere with the function and accelerate degradation of p53 and pRB, key host tumor suppressor proteins. This leaves the infected cell vulnerable to malignant transformation by loss of cell cycle control, cellular proliferation, and accumulation of DNA mutations (Doorbar, 2005).

In preinvasive lesions, normal epithelial differentiation is modified. The degree of abnormal epithelial maturation that results is used to grade lesion histology as mild, moderate, or severe cervical intraepithelial neoplasia. The average age at diagnosis of low-grade cervical disease is younger than that of high-grade lesions and invasive cancers, and it has long been assumed that a disease continuum exists. An alternative theory proposes that low-grade lesions are generally transient and non-oncogenic, whereas high-grade lesions and cancers are monoclonal, arising de novo without prerequisite low-grade disease (Baseman, 2005; Kiviat, 1996). This may explain why some cancers are diagnosed soon after negative cytologic screening.

Natural History of Human Papillomavirus Infection

Infection with HPV, predominantly HR types, is common very soon after initiation of sexual activity (Brown, 2005; Winer, 2003). However, this phenomenon is by no means confined to sexually promiscuous adolescent populations. Collins and colleagues (2002) conducted a longitudinal study of 242 women recruited within 6 months of beginning their first sexual relationship and who remained monogamous to their one sexual partner. During 3 years of surveillance, 46 percent acquired cervical HPV infection. Median time to infection was less than 3 months.

Especially in adolescents and young women, most HPV lesions, whether clinical or subclinical, spontaneously regress, (American College of Obstetricians and Gynecologists, 2005a; Fine, 1998; Ho, 1998). Several studies show that LR HPV infections resolve faster than those involving HR HPV (Moscicki, 2004; Schlecht, 2003; Woodman, 2001). Younger women frequently change HPV types, reflecting transience of infection and sequential re-infection by new partners rather than persistence (Ho, 1998; Rosenfeld, 1992).

Estimates of short-term risk of progression from incident HPV infection to high-grade neoplasia in young women range from 3 to 31 percent (Moscicki, 2004; Wright, 2005). The risk of progression to high-grade neoplasia increases with age, as HPV infection in older women is more likely to be persistent (Hildesheim, 1994).

INCIDENCE

Genital HPV is the most common sexually transmitted infection. Worldwide, populations vary in point prevalence from 2 to 44 percent. The Centers for Disease Control and Prevention (2002) estimates that the risk of a woman acquiring genital HPV by age 50 is greater than 80 percent. The prevalence of genital warts is approximately 1 percent and cytologic abnormalities 4 to 5 percent, with both more common in high-risk groups. Thus, inapparent, that is, subclinical, infection is far more common than genital warts (Koutsky, 1997). Most incident HPV infections occur in young women and adolescents under age 25.

RISK OF INFECTION

The strongest risk factors for the acquisition of genital HPV infection are the number of lifetime and recent sexual partners and early coitarche, that is, age of first sexual intercourse (Burk, 1996; Fairley, 1994; Franco, 1995; Ley, 1991; Melkert, 1993; Schiffman, 1994).

Diagnosis of Infection

Infection with HPV is suspected by the appearance of clinical lesions and through the results of cytology, histology, and colposcopy, all of which are subjective and often inaccurate. In addition, serology is unreliable and unable to distinguish past from current infection (Carter, 2000; Dillner, 1999). Therefore, a definitive diagnosis can be made only by the direct detection of HPV DNA. This

can be done histologically by in situ hybridization, by nucleic acid amplification via polymerase chain reaction (PCR), or by hybrid capture (HC) techniques (Molijn, 2005). Currently, Hybrid Capture 2 (Digene Corporation, Gaithersburg, MD) is the most common technique in clinical use. It is a chemiluminescent test that uses a mixture of RNA probes for the detection of 13 oncogenic HPV types.

Clinical HPV testing by HC 2 can be carried out by collection of cervical cells using a small brush device or in conjunction with liquid-based cytology. If a typical wart in a young woman is found or if high-grade cervical neoplasia or invasive cancer is identified by cytology or histology, then HPV infection is assumed and confirmation by HPV testing is not necessary. Routine testing for HPV is not currently indicated outside of cervical cancer screening and triage or surveillance of abnormal cytologies.

Treatment

The only indications to treat HPV-related lower genital tract disease are the presence of neoplasia or symptomatic warts that cause physical discomfort or psychological distress. Again, most HPV infection is transient, and warts have a spontaneous regression rate of 60 to 70 percent.

A variety of treatment modalities are available and are chosen according to size, location, and number of warts. Mechanical removal or destruction, topical immunomodulators, and chemical or thermal coagulation can be used (see Chap. 3, Treatment). There is no effective treatment for subclinical HPV infection. Physical damage can be done to the LGT in attempting to eradicate HPV infections, which are usually self-limited.

Examination of a male partner does not benefit a female partner either by influencing re-infection or by altering the clinical course or treatment outcome for genital warts or LGT neoplasia (Centers for Disease Control and Prevention, 2002; Howe, 2001).

Prevention

BEHAVIORAL INTERVENTIONS

Sexual abstinence, delaying coitarche, and limiting the number of sexual partners are the most logical strategies to avoid or limit genital HPV infection and its effects. However, evidence from trials of counseling and sexual practice modification is lacking.

CONDOMS

Use of condoms is recommended for prevention of sexually transmitted infections (STIs) in general, but their efficacy specifically in preventing HPV transmission is less certain. Male condoms are more effective at preventing STIs transmitted through body fluids and across mucosal surfaces, and less so for STIs spread skin-to-skin, as is the case with HPV (Centers for Disease Control and Prevention, 2002). However, Winer and associates (2003) conducted the first prospective study of male condom use and HPV risk in young women and showed reductions in HPV infection even if condoms were not consistently used.

VACCINES

Development of vaccines offers the greatest promise for prevention of HPV infection and perhaps limiting or reversing its sequelae in those already infected.

Immunology of Human Papillomavirus Infection

Immune response appears to be a key determinant of HPV epidemiology and oncogenicity. At present, the immunology of HPV is only partially characterized, but it appears that local and humoral immunity protect against initial infection. Cell-mediated immunity likely plays the larger role in HPV infection persistence, as well as progression or regression of benign and neoplastic lesions.

Prophylactic Vaccines

Prophylactic vaccines elicit humoral antibodies that neutralize HPV before it can infect host cells (Christensen, 2001). Although they do not prevent transient HPV positivity, they do prevent establishment of persistent infection and therefore, the development of cervical neoplasia.

In four randomized, masked, placebo-controlled studies totaling over 20,000 subjects, a recombinant quadrivalent vaccine against

types 6, 11, 16, and 18 (Gardasil, Merck & Co., Inc., Whitehouse Station, NJ) has shown 90- to 100-percent protection against genital warts plus vulvar, vaginal, and cervical neoplasia in women who are serology and genital tract PCR negative for the HPV types covered (U.S. Food and Drug Administration, 2006). In 2006, Gardasil received Food and Drug Administration (FDA) approval for vaccination of girls and women aged 9 to 26 years. A bivalent HPV 16/18 vaccine (Cervarix, GlaxoSmithKline, Brentford, UK) has shown similar efficacy and is anticipated to receive similar approval upon completion of its phase III trial (Harper, 2006).

Administered in three intramuscular doses during a 6-month period, both vaccines are extremely safe and well tolerated (Harper, 2006; Mao, 2006). Vaccination strategies should emphasize administration prior to coitarche when protection provided is nearly 100 percent. However, a history of previous sexual intercourse or HPV-related disease is not a contraindication to vaccine administration because exposure to the HPV types targeted by the vaccines is not certain. Testing for HPV is not recommended prior to vaccination. The Advisory Committee on Immunization Practices recommends that HPV vaccination be administered routinely to girls aged 11 to 12 years and is allowed for 9- to 26-year-old individuals whether or not they have been sexually active (American College of Obstetricians and Gynecologists, 2006b; Centers for Disease Control and Prevention, 2002).

Therapeutic Vaccines

The development of effective therapeutic vaccines for the mitigation or eradication of established HPV-related disease, including genital warts, preinvasive lesions, and invasive cancer, presents far greater challenges. The cell-mediated immunology of HPV is more complex and less understood than humoral immunity. Persistent HPV infection in any form is indication that the host-HPV interaction has evaded immune responsiveness. Current research and clinical trials are reviewed by Padilla-Paz (2005).

CERVICAL INTRAEPITHELIAL NEOPLASIA

Incidence

Of the 4 to 5 percent of Pap tests with epithelial abnormalities found annually during screening in the U.S., perhaps half represent any degree of histologic cervical intraepithelial neoplasia (CIN). The incidence of CIN will vary by population studied, as it is strongly related to younger age, socioeconomic factors, and risk-related behaviors. Moreover, its true incidence and prevalence can only be estimated, as screening cytology and colposcopy lack complete sensitivity.

Natural History

Few CIN lesions have the potential to progress to frankly invasive cancer. Progressive potential increases with CIN grade. For example, Hall and Walton (1968) observed progression to CIS in 6 percent of histologic "slight" dysplasias, 13 percent of moderate dysplasias, and 29 percent of "marked" dysplasias. Slight dysplasia regressed or disappeared in 62 percent, but did so in only 19 percent of those with marked disease. A review of natural history studies spanning 40 years and combining heterogeneous data provides estimates of CIN progression, persistence, and regression (Table 29-1) (Ostor, 1993).

Table 29-1 Natural History of Cervical Intraepithelial Neoplasia Lesions

	Regression (%)	Persistence (%)	Progression to CIS (%)	Progression to Invasion (%)
CIN 1	57	32	11	1
CIN 2	43	35	22	5
CIN 3	32	<56	â€“	>12

CIN = cervical intraepithelial neoplasia; CIS = carcinoma in situ.

From Ostor, 1993, with permission.

Risk Factors

Identifiable risk factors for cervical intraepithelial neoplasia are similar for invasive lesions and prove useful in the development of cervical cancer screening and prevention programs (Table 29-2). Ultimately, the risk of neoplasia is most strongly related to: (1)

infection with a HR HPV type, (2) older age, and (3) most importantly, persistence of the HR HPV infection (Elfgren, 2005; Ho, 1995; Koutsky, 1992; Kjaer, 2002; Lorincz, 1992; Remmink, 1995; Schiffman, 2005; Wallin, 1999). However, a constellation of other poorly defined demographic, behavioral, and medical risk factors for cervical neoplasia have been identified, varying widely among populations worldwide.

Table 29-2 Risk Factors for Cervical Neoplasia
Demographic risk factors
Ethnicity (Latin American countries, U.S. minorities)
Low socioeconomic status
Age
Behavioral risk factors
Infrequent or absent cancer screening Pap tests
Early coitarche
Multiple sexual partners
Male partner who has had multiple sexual partners
Tobacco smoking
Dietary deficiencies
Medical risk factors
Cervical high-risk human papillomavirus infection
Parity
Immunosuppression

AGE

In the United States, the median age of cervical cancer diagnosis is the middle to late forties, approximately a decade later than CIN. Theoretically, HPV infection in an older woman is more likely to be persistent than transient. Older age also allows accumulation of mutations that can lead to cellular malignant transformation. Additionally, decreased needs for prenatal care and contraception cause older women to access cancer prevention programs less often.

BEHAVIOR

The most consistently recognized behavioral risks for cervical neoplasia are noted in Table 29-2 (Brinton, 1992; Suris, 1999). Such behaviors increase the risk of acquiring oncogenic HPV infection. For many years, epidemiologic evidence has linked sexual behavior such as early coitarche, multiple sexual partners, and male partner promiscuity with cervical neoplasia (Buckley, 1981; de Vet, 1994; Kjaer, 1991).

TOBACCO SMOKING

Tobacco smoking increases the risk of cervical cancer among HPV-positive women (Bosch, 2002; Plummer, 2003). Nicotine and its major metabolite cotinine are found in the cervical mucus of women and in the semen of men who smoke. These chemicals may cause alterations that promote HPV-driven cellular transformation and neoplasia. In a case-controlled study, Becker and colleagues

(1994) implicated current smoking, high-number pack-years of use, and smoking at the time of menarche as etiologic factors associated with neoplasia. Accruing evidence may soon prompt the addition of cervical cancer to the list of tobacco-associated cancers with tobacco smoke proving to be an independent carcinogen.

DIETARY DEFICIENCIES

Although data are inconclusive, dietary deficiencies of certain vitamins such as A, C, E, beta carotene, and folic acid may alter cellular resistance to HPV infection, promoting viral infection persistence and cervical neoplasia (Paavonen, 1990). However, in the U.S., lack of association between dietary deficiencies and cervical disease may reflect the relatively sufficient nutritional status of even lower-income women (Amburgey, 1993).

MEDICAL RISK FACTORS

Combination Oral Contraception (COC) and Parity

Study results linking cervical neoplasia and these risk factors are conflicting. It has been reported that steroid hormones found in COC may affect the HPV genome and increase viral expression of oncoproteins E6 and E7 (de Villiers, 2003). During pregnancy, immunosuppression and hormonal influences on cervical epithelium combined with trauma related to vaginal deliveries have been suggested as etiologic factors associated with the development of cervical neoplasia (Brinton, 1990).

However, analysis of young women enrolled in the Atypical Squamous Cell/Low-grade Squamous Intraepithelial Lesion Triage Study (ALTS) found that noninjectable hormonal contraceptives, pregnancy, and parity had little effect on acquisition of high-risk HPV infection or development of CIN 3 (Castle, 2005). Moreover, epithelial cell cancers are generally not influenced by hormonal factors.

Immunosuppression

Studies consistently suggest that HIV-positive women have much higher rates of CIN compared with HIV-negative women (Ellerbrock, 2000; Wright, 1994). In women infected with HIV, up to 60 percent of Pap smears exhibit cytologic abnormalities and as many as 40 percent have colposcopic evidence of dysplasia. In addition, transplant recipients treated with immunosuppressive medications have a 5- to 6-percent risk of developing a neoplasm after transplantation, and most of these neoplasms are associated with oncogenic DNA viruses.

INADEQUATE SCREENING

Cervical cancer prevention requires cytologic identification and then eradication of cancer precursor or early invasive lesions. A report reviewing the screening histories of 481 women with invasive cervical cancer in Connecticut from 1985 through 1990 found that 52 percent of women had histories of suboptimal screening: 28.5 percent had never been screened, and 23.5 percent of those screened had their last Pap test 5 or more years before their cancer diagnosis (Janerich, 1995).

Differential Diagnosis and Evaluation of Cervical Lesions

In general, preinvasive lesions of the LGT are not visible to unaided inspection. The exception to this is VIN 3, which is often visible or palpable or both. Oddly, only cervical lesions at either end of the neoplastic disease spectrum are visible: condylomata and invasive cancers. Accordingly, all grossly visible cervical lesions, particularly ulcers, erosions, or leukoplakias, are justification for colposcopic examination and biopsy.

Cervical Cytology

Cervical cytologic screening is one of modern medicine's greatest success stories. The Pap test detects most cervical neoplasia during the usually prolonged premalignant or early occult malignant phases when treatment outcome is optimized.

EFFICACY OF CERVICAL CANCER SCREENING

The Pap test has never been evaluated in a randomized, controlled, or masked trial (Koss, 1989). However, countries with organized screening programs have consistently realized a dramatic decline, generally 60 to 70 percent, in both cervical cancer incidence and mortality (Noller, 2005; World Health Organization, 2006). The Pap test's specificity is consistently high, approximating 98 percent. However, estimates of its sensitivity are lower and more variable. A recent meta-analysis found a

sensitivity of 51 percent (95 percent confidence interval; 0.37 to 0.66) for detection of any grade of CIN by a single Pap test, but a higher sensitivity for high-grade lesions (Agency for Health Care Policy and Research, 2006). The Pap test is thought to be less sensitive for the detection of adenocarcinomas than for squamous lesions. Eighty percent of cervical cancers are squamous, whereas 15 percent are adenocarcinomas (Moore, 2006).

Women should be aware of the imperfect sensitivity of the Pap test and the need for periodic screening to compensate. Providers likewise should use the Pap test appropriately as a screening test in asymptomatic women. Physical signs or symptoms suspicious for cervical cancer should be evaluated with diagnostic studies such as colposcopy and biopsy.

Although up to 70 percent of cervical cancer cases in screened populations are associated with either inadequate screening or surveillance of abnormal results, 30 to 40 percent develop in screened women (Carmichael, 1984). False-negative Pap tests may result from sampling error, in which abnormal cells are not present in the Pap test; from screening error, in which the cells are present but missed by the screener; or from interpretation error, in which abnormal cells are misclassified as benign (Wilkinson, 1990). Although quality assurance measures and new computerized screening technologies address the latter two factors, clinicians can favorably impact the sensitivity of the Pap test by obtaining an optimal cytologic specimen.

CERVICAL SCREENING TECHNOLOGIES

Conventional Pap Collection

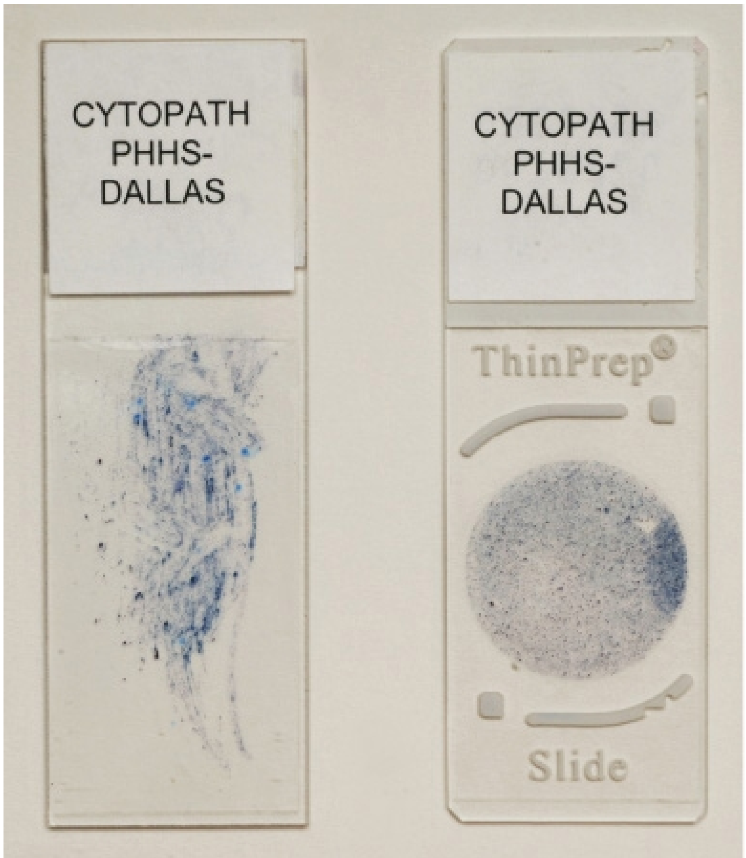
There are presently two cervical cytology techniques in use: conventional and liquid-based. The conventional Pap test is a smear of cells made directly from collection device to glass slide at the time of sampling. Goodman and Hutchinson (1996) demonstrated that most cellular material remains on the collection device and is discarded after a single conventional smear is prepared. Although examination of the excess material ordinarily discarded did not result in additional diagnoses of HSIL or cancer, the discarding of most cervical material sampled has raised concern with this method.

Liquid-Based Pap Collection

The imperfect sensitivity and variable smear quality of conventional Pap collection have driven the development of thin-layer liquid-based cytology (LBC) during the past decade. Liquid-based cytology collects cells in a liquid transport medium that is subsequently processed to produce an even monolayer of cells on a glass slide. There are currently two LBC products marketed in the U.S.: ThinPrep 2000 (Cytyc Corp., Boxborough, MA) and SurePath (TriPath Imaging, Inc., Burlington, NC). Both products are FDA approved as alternatives to the conventional Pap test.

The number of cells, between 50,000 and 75,000, and the area of the slide covered with cells are less than with a conventional smear. However, obscuring blood, mucus, debris, and cellular overlap are largely eliminated. Theoretically, abnormal cells that might be few in number, clustered, and obscured on a conventional smear will be randomly and evenly distributed over the area of the LBC slide and thus be more visible for detection (Fig. 29-5). In addition, most or all of the collected cellular material is available for laboratory processing and is not discarded in the sampling process.

FIGURE 29-5



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Conventional cervical cytology is prepared by smearing collected cells directly onto a glass slide with the collection device followed by immediate fixation (**left slide**). Thin-layer liquid-based cytology involves transfer of collected cells from collection device into a liquid transport medium with subsequent processing and transfer onto a glass slide. Cells are distributed over a smaller area and debris, mucus, blood, and cell overlap are largely eliminated (**right slide**). *(Courtesy of Dr. Raheela Ashfaq.)*

Residual LBC specimens can undergo testing for HPV, herpes simplex virus, *Neisseria gonorrhoeae,* and *Chlamydia trachomatis.* ThinPrep is FDA approved for reflex HPV testing and it is possible that SurePath will gain similar approval in the future.

PERFORMING A PAP TEST

Preparation

Ideally, Pap tests should be scheduled to avoid menstruation. Patients should abstain from vaginal intercourse, douching, and use of vaginal tampons and medicinal or contraceptive cream preparations for a minimum of 24 to 48 hours before a test. Treatment of cervicitis or vaginitis prior to Pap testing is optimal. However, Pap testing should never be deferred due to unexplained inflammatory conditions or bleeding, as these signs and symptoms may be caused by cervical or other genital tract cancers. Pap screening should be performed on high-risk patients whenever an opportunity arises.

Complete clinical information is essential to accurate interpretation of a Pap test and includes documenting the date of last menstrual period or pregnancy, exogenous hormone use, menopausal status, and past history of abnormal bleeding or abnormal Pap test results, dysplasia, or cancer. Additionally, intrauterine devices (IUDs) can cause reactive cellular changes and their use should be noted. Important risk factors such as immunosuppression, recent immigration from an underdeveloped country, or prior

lack of adequate screening may be helpful.

Adequate visualization of the cervix is essential for detection of gross lesions and identification of the SCJ. Touching the cervix should be avoided prior to performing a Pap, as dysplastic epithelium, particularly high-grade lesions, may be inadvertently removed with minimal trauma. Discharge covering the cervix may be carefully removed with a large swab, preferably without touching the cervix. Vigorous blotting or rubbing may cause scant cellularity or a falsely negative Pap test result. When indicated, additional cervical sampling to detect infection should be performed after Pap testing.

Location

Sampling of the transformation zone is paramount to the sensitivity of the Pap test. Technique should be adapted and sampling devices chosen according to the location of the squamocolumnar junction which varies widely with age, obstetric trauma, and hormonal status (Squamocolumnar Junction). Women known or suspected of in utero DES exposure may also benefit from a separate Pap test of the upper vagina, as these women are at additional risk for vaginal cancers (see Chap. 18, Acquired Uterine Defects) (Kaufman, 2005; Palmer, 2002).

Sampling Tools

Three types of devices are commonly used to sample the cervix: the spatula, the broom, and the endocervical brush (Saslow, 2002; Spitzer, 1998). A spatula predominantly samples the ectocervix. An endocervical brush samples the endocervical canal and is used in combination with a spatula. A broom samples both endo- and ectocervical epithelia simultaneously.

A spatula is oriented to best fit the cervical contour, straddle the squamocolumnar junction, and sample the distal endocervical canal. A clinician firmly scrapes the cervical surface completing at least one full rotation. For spatulas, plastic is preferred to wood because cells are more easily released from a plastic surface.

The endocervical brush, with its conical shape and plastic bristles, has largely replaced the moistened cotton swab to sample the endocervical canal because of its superior ability to collect and release endocervical cells (Koonings, 1992; Martin-Hirsch, 2001; Taylor, 1987). After the spatula sample is obtained, the endocervical brush is inserted into the endocervical canal only until the outermost bristles remain visible. This prevents inadvertent sampling of lower uterine segment cells, which can appear falsely atypical. To avoid excessive bleeding, the brush is rotated only one-quarter to one-half turn. If the cervical canal is wide, as in parous women, the brush is moved to contact all surfaces of the entire endocervical canal.

Broom devices have longer central bristles that are inserted into the endocervical canal. These longer bristles are flanked by shorter bristles that splay out over the ectocervix during multiple clockwise rotations. The recommended number of broom rotations varies by manufacturer. Broom devices are favored for LBC.

Conventional Slide Testing

This cytology method requires special care to avoid air drying of cells, a leading cause of poor slide quality. The spatula sample should be held while the endocervical brush sample is taken. The spatula sample is then quickly spread as evenly as possible over one half to two thirds of a glass slide. The endocervical brush is firmly rolled over the remaining area of the slide, after which fixation is carried out immediately by spray or immersion.

Liquid-Based Testing

Sampling and cell transfer to a liquid medium should be performed according to manufacturer specifications. SurePath allows for the use of all three device types, but with modified device tips that can be broken off and sent to the laboratory in the liquid medium. ThinPrep requires immediate and vigorous agitation of the chosen collection device in the liquid medium, after which the device is discarded.

COMPARISON OF CONVENTIONAL AND LIQUID-BASED CYTOLOGY

Liquid-based cytology now accounts for most of Pap tests performed in the U.S. Both LBC products are FDA-approved to claim a 65-percent increased detection rate of HSIL compared with conventional smears, as well as decreased unsatisfactory sample rates. Furthermore, there is evidence that LBC is more sensitive and accurate for the detection of both squamous lesions and adenocarcinomas of the cervix (Ashfaq, 1999; Chhieng, 2004). Comparison studies show variable results with respect to atypical

squamous cell detection rates.

Although the preponderance of numerous studies show an increase in sensitivity by LBC technology, controversy exists about data significance because of study methodologies (Baker, 2002; Bernstein, 2001; Braly, 2001; Hutchinson, 1999). Ronco and colleagues (2006) have published the first randomized controlled trial that compares conventional Pap testing to LBC in a screening population. Although LBC decreased the unsatisfactory Pap rate, its sensitivity was similar to that of conventional Pap tests, but with a lower positive predictive value. The deficiencies of comparative data, uncertainties of cost effectiveness, and potential adverse consequences of decreased specificity with LBC have been reviewed elsewhere (Davey, 2006; Sawaya, 1999; Spitzer, 1998).

SCREENING GUIDELINES

Current cervical cancer screening guidelines are more evidence-based and comprehensive than in the past. The three agencies offering guidelines are the American College of Obstetricians and Gynecologists, the American Cancer Society (ACA), and the U.S. Preventive Services Task Force (USPSTF) (Table 29-3) (American College of Obstetricians and Gynecologists, 2003; Saslow, 2002; U.S. Preventive Services Task Force, 2006).

Table 29-3 Cervical Cytology Screening Guidelines

	ACS	ACOG	USPSTF
Initiation of screening	Approximately 3 years after onset of vaginal intercourse; no later than age 21	See ACS	See ACS
Screening intervals for women at average risk	Age ≤30: annual if conventional smear; every 2 years if LBC test	Age ≤30: annual	At least every 3 years
	Age >30: every 2 to 3 years after 3 consecutive negative tests	Age >30: see ACS	
Screening intervals for women at higher risk	HIV + or other immunocompromised state: 2 tests during first year after immune disease diagnosis, then annually (per CDC)	HIV +: see ACS Other immunocompromised states, DES: may require more frequent screening	No specific recommendations
		History of CIN 2 or 3 or cervical cancer: annual	
Discontinuation of screening	Age 70: consider if 3 documented negative (and no abnormal) tests in prior 10 years	Age 70 in low-risk women	Age 65 if not otherwise at high risk for cervical cancer
	Continue if screening history uncertain, history of cervical cancer, DES, recent HPV +, HIV + status, other immunocompromised state	Continue if high risk, sexually active, history of multiple sexual partners, or history of abnormal cytology	
Screening after hysterectomy	Not indicated if removal confirmed for benign indication Subtotal hysterectomy: continue screening per guidelines	Not indicated if removal confirmed with benign pathology and past negative cytologies	Not recommended if total hysterectomy for benign disease
	Continue screening if history of DES or cervical cancer	See ACS	See ACS

	cervical cancer	Positive or uncertain history of CIN 2 or 3: annual screening until 3 negative tests obtained, then may discontinue	

ACOG = American College of Obstetricians and Gynecologists; ACS = American Cancer Society; CDC = Centers for Disease Control and Prevention; CIN = cervical intraepithelial neoplasia; DES = in utero diethylstilbestrol exposure; HIV+ = human immunodeficiency virus infection positivity; HPV+ = human papillomavirus DNA positivity; LBC = liquid-based cytology; USPSTF = U.S. Preventive Services Task Force.

Data from American College of Obstetricians and Gynecologists, 2003, Saslow, 2002, and U.S. Preventive Services Task Force, 2003, with permission.

Initiation of Screening

Cervical cancer does occur in adolescents, but it is rare. Accordingly, screening should begin approximately 3 years after coitarche or by age 21, whichever occurs first. Screening by age 21 regardless of sexual history protects those who are unwilling or unable to reveal sexual activity, whether consensual or resulting from abuse or assault. The 3-year window after coitarche recognizes that high-grade cervical neoplasia and cancer usually take several years to develop after exposure to HPV and avoids unnecessary detection of transient HPV infections and low-grade neoplastic lesions in adolescents (Moscicki, 1998). Earlier commencement of screening is acceptable at the discretion of the health care provider.

After age 30, women at average risk for cervical cancer can be screened at 2- to 3-year intervals if three consecutive, annual negative Pap tests have been documented. Women at higher risk due to prior treatment for CIN 2, CIN 3, or cervical cancer, in utero DES exposure, or immunosuppressive illness or medications should receive at least annual screening. Specifically, HIV-infected women require a Pap test twice during the first year after diagnosis and annually thereafter (Centers for Disease Control and Prevention, 2002).

These guidelines should not preclude or delay other indicated gynecologic care. Supplying contraception and other medical therapies should not be contingent upon compliance with cervical cancer screening recommendations or evaluation of cytologic abnormalities, especially for adolescents.

Discontinuation of Screening

Screening may be stopped at age 65 or 70 in women not at high risk for cervical cancer. Similarly, vaginal cancers are rare, accounting for less than 2 percent of cancers in women, and screening in most women who have undergone total hysterectomy for benign disease may be halted (Saraiya, 2001; Sirovich, 2004).

HPV TESTING FOR PRIMARY CERVICAL CANCER SCREENING

In 2003, the FDA approved the use of the Hybrid Capture 2 test for HR HPV in combination with cytology for cervical cancer screening in women aged 30 years and older. The combination of HPV DNA testing with cytology increases the sensitivity of a single Pap test for high-grade neoplasia from 50 to 85 percent, to nearly 100 percent (American College of Obstetricians and Gynecologists, 2005b). In women younger than 30 years, the high prevalence of HR HPV infection makes this strategy too nonspecific for use.

For primary screening, a cervical sample for HPV can be sent in a collection device separate from the cytology specimen. This allows simultaneous processing of the two components.

The increased sensitivity and acceptable specificity of HPV DNA testing combined with cervical cytology for women age 30 years and older eliminates the need for annual screening in this age group and is cost effective (Wright, 2004). If both tests are negative, they are not to be repeated in less than 3 years regardless of a history of new sexual partners. The chance of cervical cancer being present or developing during a 3-year screening period is extremely low, at approximately 1 in 1,000 (American College of Obstetricians and Gynecologists, 2005b, Wright, 2007a).

Evidence-based guidelines have been developed for management of an abnormal HPV DNA test plus cytology results (Wright,

2007a). If cytology is abnormal, current cytology management guidelines are followed (Epithelial Cell Abnormalities: Significance and Management). Cytology-negative and HPV-positive test results will occur in less than 7 percent of screened patients. In such cases, it is recommended that cytology and HPV DNA testing be repeated 12 months later. Colposcopy is recommended for persistently positive HPV DNA test results. An abnormal repeat cytology result is managed according to current guidelines.

THE 2001 BETHESDA SYSTEM

In 1988, standardization of cervical cytology reporting took place with the development of the Bethesda System nomenclature (National Cancer Institute Workshop, 1989). Subsequent revisions led to the 2001 Bethesda System for reporting cervical cytology results. Its components are seen in Table 29-4 (Solomon, 2002). Clinically, the key elements are assessment of specimen adequacy and epithelial cell abnormalities (Table 29-5).

Table 29-4 The 2001 Bethesda System Cytology Report Components
Specimen type
Conventional Pap test
Thin-layer liquid-based cytology
Specimen adequacy
Satisfactory for evaluation
Unsatisfactory for evaluation
General categorization (optional)
Negative for intraepithelial lesion or malignancy
Epithelial cell abnormality
Other findings that may indicate increased risk
Interpretation of results
Negative for intraepithelial lesion or malignancy
Organisms:
Trichomonas vaginalis
Fungal organisms consistent with *Candida* species
Shift in flora suggestive of bacterial vaginosis
Cellular change consistent with herpes simplex virus
Bacteria consistent with *Actinomyces* species
Other non-neoplastic findings (optional)
Reactive cellular changes (inflammation, repair, radiation)
Glandular cells posthysterectomy

Atrophy
Epithelial cell abnormalities
Squamous cell
Glandular cell
Other:
Endometrial cells in a woman ≥40 years of age
Automated review and ancillary testing as appropriate
Educational notes and recommendations (optional)

From Solomon, 2002, with permission.

Table 29-5 The 2001 Bethesda System: Epithelial Cell Abnormalities
Squamous cell
Atypical squamous cells (ASC) of undetermined significance (ASC-US) cannot exclude HSIL (ASC-H)
Low-grade squamous intraepithelial lesion (LSIL)
High-grade squamous intraepithelial lesion (HSIL)
Squamous cell carcinoma
Glandular cell
Atypical glandular cells (AGC)
Endocervical, endometrial, or not otherwise specified
Atypical glandular cells, favor neoplastic
Endocervical or not otherwise specified
Endocervical adenocarcinoma in situ (AIS)
Adenocarcinoma

From Solomon, 2002, with permission.

Specimen Adequacy

Specimen adequacy is reported as satisfactory or unsatisfactory for evaluation, based primarily on criteria for slide cellularity and the presence of obscuring blood or inflammation. The presence of transformation zone (TZ) components (endocervical or squamous metaplastic cells or both) is evidence that the area at risk has been sampled, but is no longer requisite for adequacy. Notation is made as to their presence or absence. Their presence is associated with increased detection of cytologic abnormalities, but their absence is not reported to be associated with failure to diagnose CIN. Pap tests lacking TZ components or partially obscured by blood or inflammation should be repeated in 1 year or earlier if clinically indicated by individual risk factors and adequacy of past

screening (American College of Obstetricians and Gynecologists, 2003; Saslow, 2002). Rarely, obscuring blood and inflammation on cervical cytology indicate the presence of invasive cancer. Therefore, presence of an unexplained vaginal discharge, abnormal bleeding, or abnormal physical findings should prompt immediate evaluation rather than awaiting repeat Pap testing.

Epithelial Cell Abnormalities: Significance and Management

A cytology report is a medical consultation that interprets a screening test and is not a diagnosis. Thus, a final diagnosis is determined clinically, often with results from histologic evaluation.

Pap tests are interpreted as either negative for intraepithelial lesion or malignancy, or consistent with one or more epithelial cell abnormalities. To address abnormal findings, evidence-based management guidelines have been developed and are summarized in Table 29-6 (American College of Obstetricians and Gynecologists, 2005a; Wright, 2007a). Alternative management strategies may be appropriate based on individual patient characteristics, available resources, and other clinical factors.

Table 29-6 Cervical Cytology: Initial Management of Epithelial Cell Abnormalities

Epithelial Cell Abnormality	General Recommendation	Special Circumstances
ASC-US	Repeat cytology at 6 and 12 months Reflex HPV DNA testing Colposcopy	Refer to colposcopy for recurrent abnormal cytology, or initial positive HPV DNA test; adolescents[b] managed with repeat annual cytology
LSIL	Colposcopy for non-adolescent women	Adolescents managed with repeat annual cytology; HPV DNA test at 12 months or repeat cytology at 6 and 12 months are also acceptable for postmenopausal women
ASC-H, HSIL, squamous cell carcinoma	Colposcopy	
AGC, AIS, adenocarcinoma	Colposcopy, endocervical curettage[a] ; HPV DNA testing for AGC	Endometrial sampling[a] indicated if age >35 years, abnormal bleeding, chronic anovulation, or atypical endometrial cells specified

[a] Endocervical curettage and endometrial sampling are contraindicated in pregnancy.

[b] adolescents = age 13 to 20 years.

AGC = atypical glandular cells; AIS = adenocarcinoma in situ; ASC-H = atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; ASC-US = atypical squamous cells of undetermined significance; HPV = human papillomavirus; HSIL = high-grade squamous intraepithelial lesion; LSIL = low-grade squamous intraepithelial lesion.

Adapted from Wright, 2007a, with permission.

Atypical Squamous Cells of Undetermined Significance

The most common cytologic abnormality is atypical squamous cells of undetermined significance (ASC-US), which indicates cells that are suggestive of, but do not fulfill the criteria for, SIL. Although an ASC-US result often precedes the diagnosis of CIN 2 or 3, this risk approximates only 5 percent and cancer is found in only 1 to 2 per thousand instances (Solomon, 2002). Therefore, the evaluation of ASC-US should not be overly aggressive, particularly in adolescents who are at low risk of cervical cancer (American College of Obstetricians and Gynecologists, 2006a; Moscicki, 2005).

Three options for evaluation of ASC-US are HPV DNA testing, colposcopy, or repeat cytologies at 6 and 12 months, with referral to colposcopy if either of these is abnormal (Wright, 2007a). If LBC is used, reflex HPV DNA testing from the same specimen is preferred. If high-risk HPV DNA types are found, colposcopy is indicated, as risk of CIN 2 or worse is equal to that of LSIL cytology.

If high-risk HPV DNA is absent, then a subsequent Pap test in 12 months is recommended. Alternatively, immediate colposcopy may be considered in certain patients, such as those who are unlikely to be compliant with further testing.

ASC-US cytologies are evaluated differently in adolescents age 20 years and younger due to a higher rate of HPV positivity, the rarity of cervical cancer, and the high rates of spontaneous regression of cervical neoplasia in this group. (Boardman, 2005; Wright, 2006). Reflex HPV testing should not be done. Instead, annual repeat cytology should be obtained and colposcopy performed only with a high-grade cytology result or if any cytologic abnormality persists at 2 years (Wright, 2007a).

Atypical Squamous Cells, Cannot Exclude HSIL

Five to 10 percent of ASC is designated as atypical squamous cells, cannot exclude high grade (ASC-H). This describes cellular changes that do not fulfill criteria for HSIL cytology, but for which a high-grade lesion cannot be excluded. Histologic HSIL is found in upwards of 25 percent of these cases. This is higher than that seen with ASC-US, and therefore colposcopy is indicated for evaluation (Wright, 2003, Wright 2007a).

Low-Grade Squamous Intraepithelial Lesion

This cytology result indicates the likely presence of HPV infection or low-grade neoplasia. Low-grade SIL encompasses the cytologic features of HPV infection and CIN 1 and carries a 15 to 30 percent risk of CIN 2 or 3, similar to the ASC-US HPV-positive category. Therefore, colposcopy is indicated for most. HPV testing is not useful in reproductive-aged women, as approximately 80 percent will test positive for HPV DNA (ALTS Group, 2000). Adolescents with LSIL should initially be managed with repeat cytology as with ASC-US. Due to a lower positive predictive value of LSIL cytology for CIN 2 or 3 and a lower rate of HPV positivity in postmenopausal women, alternative management of LSIL includes reflex HR HPV testing or repeat cytology at 6 and 12 months. HPV positivity or abnormal repeat cytology are indications for colposcopy.

High-Grade Squamous Intraepithelial Lesion and Glandular Abnormalities

High-grade SIL, all glandular epithelial cell abnormalities, and suspicion of carcinoma should all be evaluated by prompt colposcopic evaluation. High-grade SIL cytology encompasses features of CIN 2 and CIN 3 and carries a high risk of underlying histologic CIN 2 or CIN 3 (at least 70 percent), or invasive cancer (1 to 2 percent) (Kinney, 1998). Alternative management of HSIL cytology in women age 21 years and older includes immediate diagnostic loop excision because colposcopy may miss a high-grade lesion and most HSIL cytologies eventually result in excision for diagnosis or treatment. HPV DNA testing is not useful in the management of HSIL cytology.

As reviewed by Schnatz and associates (2006), squamous neoplasia is the most common diagnosis found upon evaluation of atypical glandular cell (AGC) cytology, but there is also a high risk of both endocervical and endometrial, as well as other reproductive tract cancers. Therefore, colposcopic evaluation of a glandular abnormality should include endocervical sampling in nonpregnant patients. Endometrial biopsy is indicated in women older than 35 years or in those younger if there is a history of abnormal bleeding, if risk factors for endometrial disease are noted, or if the cytology indicates that the atypical glandular cells are of endometrial origin.

If colposcopy and biopsies are without evidence of neoplasia, management of glandular abnormalities is generally more aggressive than for other abnormalities due to a higher risk of occult disease. Current consensus guidelines should be followed (Wright, 2007a). Surveillance may include post-colposcopy HPV testing, repeat cytologies, or excision, depending on the glandular abnormality and other clinical factors.

NON-NEOPLASTIC FINDINGS

Certain non-neoplastic findings may be reported, including findings consistent with, but not conclusively diagnostic of, certain organisms. These findings include *Trichomonas vaginalis, Candida* species, *Actinomyces* species, herpes simplex virus, or flora consistent with bacterial vaginosis. Confirmatory tests or clinical correlation should dictate any action related to these findings. Other non-neoplastic findings are reactive changes associated with inflammation or repair, radiation, changes, benign glandular cells posthysterectomy, and atrophy. None of these warrant a specific action on the part of the clinician.

Because the menstrual history of a woman is often unknown to the cytologist, endometrial cells that appear benign are reported on

Pap reports for all women aged 40 years and older. As reviewed by Browne and colleagues (2005), the need for evaluation in normally menstruating women has been controversial and therefore individualized according to clinical history and risk factors. The 2006 consensus guidelines recommend that no evaluation is needed in an asymptomatic premenopausal woman (Wright 2007a). However, postmenopausal women, and those with abnormal bleeding or the presence of other risk factors for endometrial disease should undergo further evaluation of the endometrium (see Chap. 8, Endometrial Biopsy).

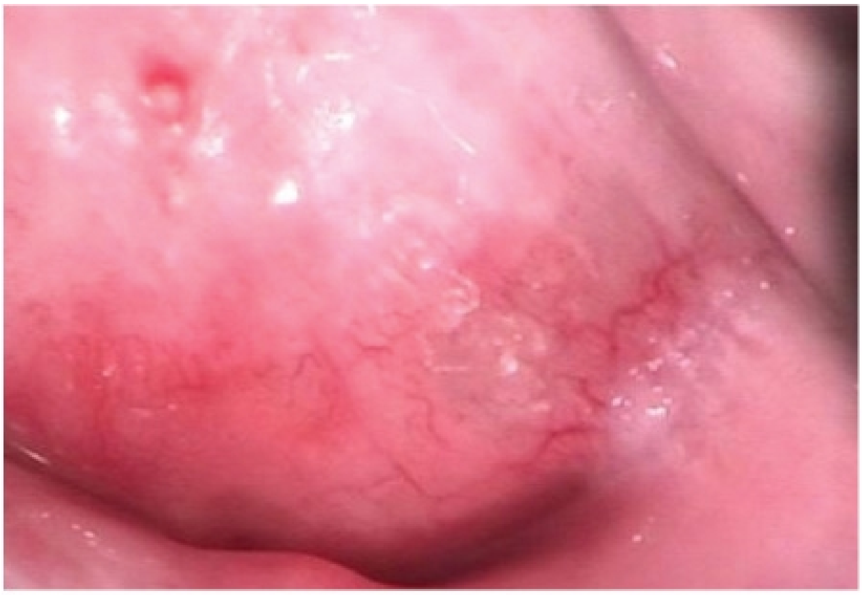
Colposcopy

Colposcopy is an outpatient procedure that is simple, quick, and well-tolerated. It allows examination of the lower genital tract and anus with a microscope to further evaluate abnormal Pap test results and visible epithelial abnormalities. This allows identification and management of premalignant lesions. Colposcopic examination of the cervix remains the clinical standard in the evaluation of patients with abnormal cervical cytology. However, its sensitivity, interobserver agreement, and reproducibility have recently come into question (Ferris, 2005).

COLPOSCOPE

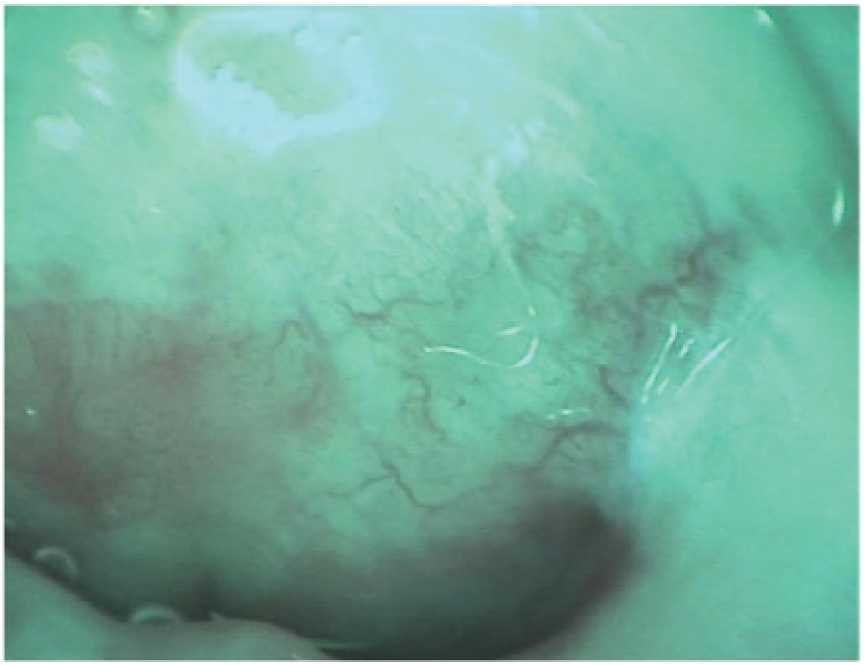
There are many styles of colposcopes, but they all operate similarly. The colposcope consists of a stereoscopic viewing system with magnification settings ranging from three- to 40-fold attached to a freely moveable stand. A high-intensity halogen light provides illumination. Use of a green (red-free) light filter emphasizes contrast by causing the color red to appear black, aiding the examination of vascular patterns (Fig. 29-6).

FIGURE 29-6



A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



A. Benign surface vessels viewed through a colposcope using usual white light source. **B.** Use of a blue-green (red-free) light filter provides higher contrast and definition of vascular patterns.

PREPARATION

Prior to colposcopic examination, a woman's medical record, including past gynecologic and dysplasia histories, should be reviewed and indications for colposcopy confirmed (Table 29-7) (Epithelial Cell Abnormalities: Significance and Management). Urine pregnancy testing is warranted for sexually active patients who may be pregnant. Colposcopic examination is optimally timed to avoid menses. However, it should be performed despite menstruation if a gross lesion suspicious for invasive cervical carcinoma is seen, if a patient is noncompliant, or if there is a history of abnormal bleeding that may be mistaken as menstrual bleeding.

Table 29-7 Clinical Considerations Directing Colposcopy

Clinical objectives
Provide a magnified view of the lower genital tract
Identify squamocolumnar junction of the cervix
Detect lesions suspicious for neoplasia
Direct biopsy of lesions
Monitor patients with a current or past history of lower genital tract neoplasia
Clinical indications
Grossly visible genital tract lesions
Abnormal cervical cytology
History of in utero diethylstilbestrol exposure
Contraindications
None
Relative contraindications
Anticoagulant therapy if patient requires biopsy
Upper or lower reproductive tract infection
Uncontrolled severe hypertension
Uncooperative or overly anxious patient

A Pap test at the time of colposcopy is of questionable value and should be performed on an individualized basis. A saline wet prep, cervical culture, and treatment of an identified pathogen may be indicated in cases of severe cervicitis before performing biopsies or endocervical curettage.

SOLUTIONS

Normal Saline

Saline helps remove cervical mucus and allows vascular and surface features of lesions to be initially assessed. Abnormal vessels, especially when viewed with green filtered light, may be more prominent without acetic acid application.

Acetic Acid

Also known as white table vinegar, acetic acid is a mucolytic agent that reversibly clumps nuclear chromatin causing lesions to assume various shades of white depending on the resultant degree of abnormal chromatin density. Applying 3- to 5-percent acetic acid to mucosal epithelium results in the *acetowhite* change characteristic of neoplastic lesions as well as some non-neoplastic conditions.

Lugol Solution

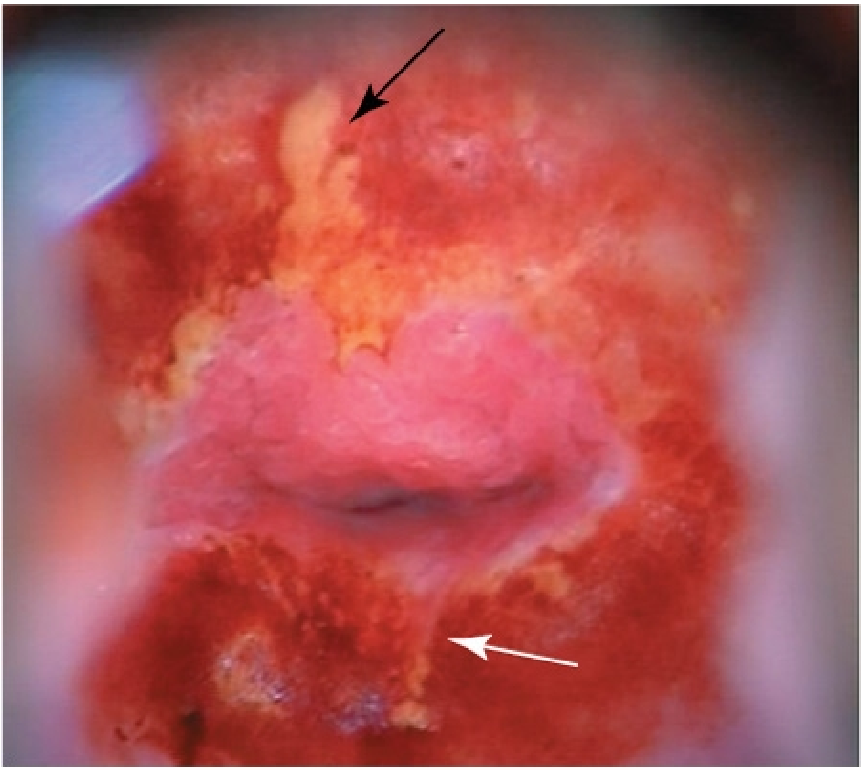
Lugol iodine solution stains mature squamous epithelial cells mahogany in estrogenized women due to high cellular glycogen content. Due to attenuated cellular differentiation, dysplastic cells have lower glycogen content and fail to fully stain, appearing

various shades of yellow (Fig. 29-7). Lugol solution should not be used in patients allergic to iodine, radiographic contrast, or shellfish. Lugol solution is particularly useful when abnormal tissue cannot be found using acetic acid alone, and to better define the limits of the transformation zone.

FIGURE 29-7

A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

A. Cervix after application of acetic acid. Several areas of acetowhite change adjacent to the squamocolumnar junction are apparent. **B.** Same cervix after application of Lugol iodine solution. Non-staining of the lesions at the 10 to 11 o'clock positions is seen (**black arrow**) while there is partial iodine uptake of acetowhite areas along the posterior SCJ (**white arrow**).

COLPOSCOPIC GRADING

Colposcopists are trained to discriminate between normal and abnormal tissue for biopsy purposes. Several colposcopic grading systems that quantify various colposcopic signs have been developed to improve accuracy (Coppleson, 1993; Reid, 1985). Best known, the Reid Colposcopic Index (RCI) has a reported histologic correlation of 97 percent. The RCI is based upon four colposcopic lesion features: *peripheral margin, color, vascular patterns,* and *Lugol solution (iodine) staining.* Each category is scored from zero to two and the summation provides a numeric index which correlates with histology (Table 29-8).

Table 29-8 Reid Colposcopic Index			
Colposcopic Sign	**Zero Points**	**1 Point**	**2 Points**
Margin	Condylomatous Micropapillary Feathery Satellite lesions	Smooth Straight	Rolled Peeling Internal border
Color: acetowhitening	Shiny Snowy Translucent Transient	Duller white	Dull white Gray
Vessels	Fine patterns Uniform caliber and patterns	Absent	Coarse patterns Dilated with variable caliber and intercapillary distances
Iodine staining	Positive	Partial	Negative

Adapted from Reid, 1985, with permission.

Lesion Margins and Color

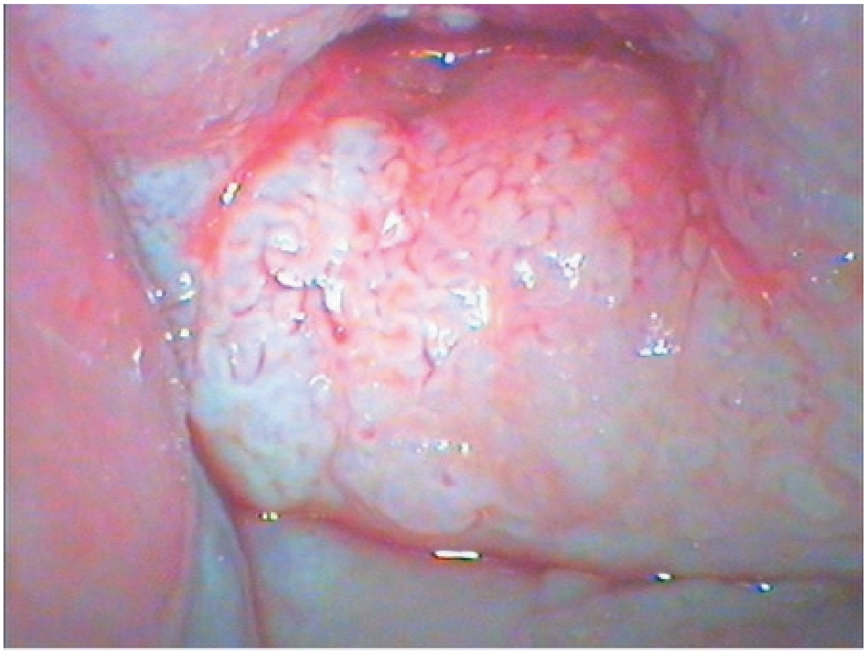
Following application of 3- to 5-percent acetic acid to mucosal epithelium, the color or degree of whiteness obtained, rapidity and duration of acetowhitening, and sharpness of lesion borders are observed. High-grade lesions demonstrate a more persistent, duller shade of white, whereas low-grade lesions are translucent or bright white and fade quickly. Low-grade lesions characteristically have feathery margins, whereas high-grade lesions have straighter, sharper outlines (Figs. 29-8 and 29-9). A lesion with an internal border, that is, a lesion within a lesion, is typically high-grade.

FIGURE 29-8

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Low-grade squamous intraepithelial lesion. Seen after 5-percent acetic acid application, lesions are often multifocal and bright white with irregular borders.

FIGURE 29-9



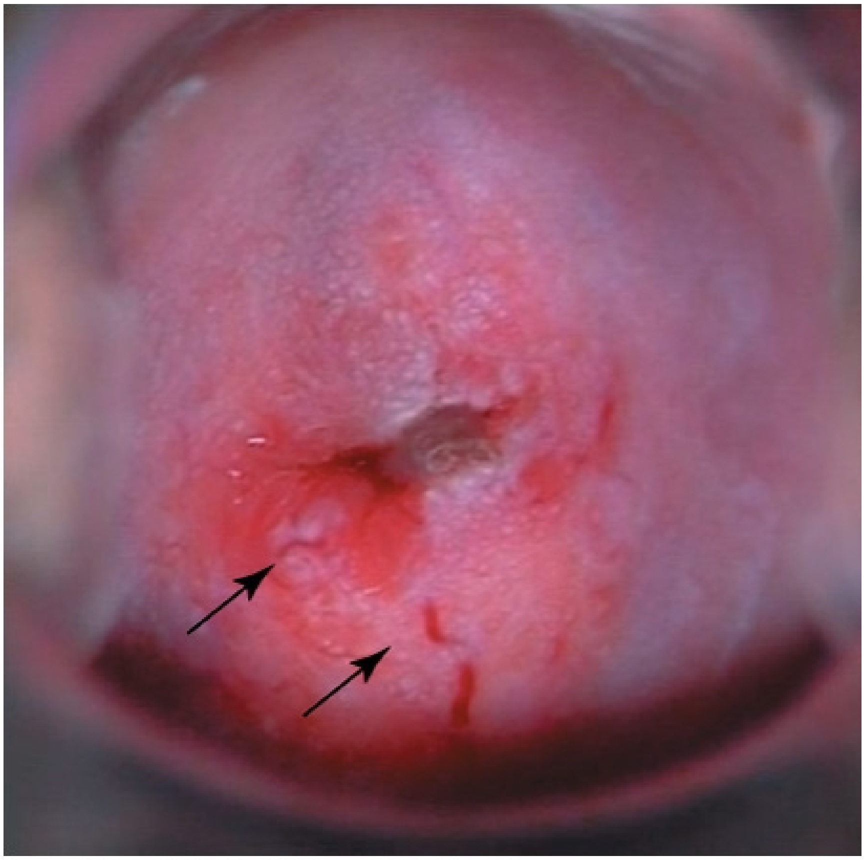
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

High-grade squamous intraepithelial lesion. CIN 3 lesion after 5-percent acetic acid application demonstrating large size, well-defined borders, off-white dull coloration, and coarse vascular pattern.

Lesion Vascular Patterns

The vascular patterns associated with abnormal epithelium include punctation, mosaicism, and atypical vessels. Punctate and mosaic patterns are graded on the basis of vessel caliber, intercapillary distance, and the uniformity of each of these. Fine punctation and mosaicism, which are created by narrow vessels and uniform intercapillary distances, typify low-grade lesions. A coarse pattern results from wider and more variable vessel diameter and spacing. This indicates higher-grade abnormalities, whereas mosaic "tiles" with a central punctation indicate carcinoma in situ (CIS). Atypical vessels are terminal vessels that are irregular in size, shape, course, and arrangement (Fig. 29-10). These should raise the suspicion of cancer.

FIGURE 29-10



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

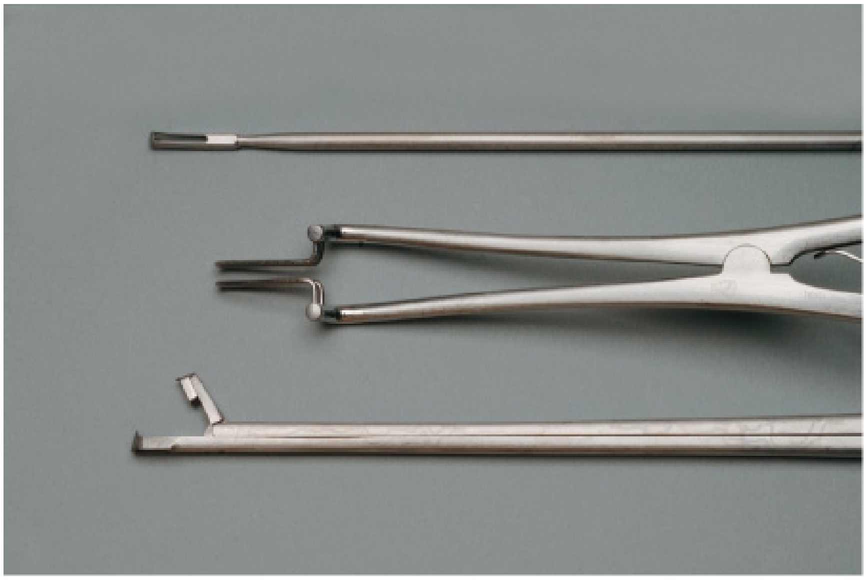
Mosaic vascular pattern with atypical vessels (**arrows**).

BIOPSY

Ectocervical Biopsy

Under direct colposcopic visualization, suspicious lesions on the ectocervix are biopsied using a sharp instrument such as a Tischler biopsy forceps (Fig. 29-11). Generally, cervical biopsy does not require an anesthetic. Thickened Monsel solution (ferric subsulfate) or a silver nitrate applicator, applied with pressure to the biopsy site, provides hemostasis. Extreme cases of bleeding are rare and can be controlled with vaginal packing.

FIGURE 29-11



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

From top to bottom, endocervical curette, endocervical speculum, and a cervical biopsy forceps.

Satisfactory Colposcopy

Within a neoplastic lesion, more severe disease tends to be at the proximal limit of the transformation zone. Thus, adequate visualization of the entire cervical SCJ and upper limits of all lesions defines whether a colposcopic examination is termed *satisfactory* or *unsatisfactory.* This determination can affect management. Therefore, with initially unsatisfactory colposcopy, an endocervical speculum may be used to dilate and fully visualize lesions that have extended cephalad into the endocervical canal (Fig. 29-12).

FIGURE 29-12

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Use of an endocervical speculum to visualize the endocervical canal during colposcopy.

Endocervical Curettage

For nonpregnant patients, endocervical curettage (ECC) is used to evaluate tissue within the endocervical canal not visualized by colposcopy. A normal ECC provides an added degree of assurance that a neoplastic endocervical lesion is not present (Grainger, 1987). Despite its common use, there are no randomized trials supporting the performance of ECC routinely during colposcopy (Abu, 2005).

Endocervical curettage generally is performed at the time of colposcopic assessment of an abnormal Pap test if:

- Colposcopy is unsatisfactory, which is common in postmenopausal women (Dinh, 1989)
- Atypical glandular cell cytology is evaluated (Granai, 1985; Wright, 2007a)
- Ablative treatment is planned (Husseinzadeh, 1989)
- Conization for adenocarcinoma in situ has been performed. During surveillance of these women, Schorge and associates (2003) found that negative ECC results may postpone repeat conization or definitive hysterectomy in women wanting to preserve fertility.

Endocervical curettage is performed by introducing an endocervical curette 1 to 2 cm into the cervical canal (see Fig. 29-11). The entire length and circumference of the canal is firmly curetted, carefully avoiding sampling of the ectocervix or lower uterine segment. Endocervical scrapings admix with cervical mucus, which may be removed using ring forceps or a cytobrush and included with the curettage specimen. Alternatively, a cytobrush may be used to obtain an endocervical tissue specimen.

Management of Histologic Cervical Intraepithelial Neoplasia

Management of CIN falls into two general categories: observation and treatment. The objective of all treatment is surgical obliteration of the entire cervical transformation zone, including abnormal tissue. This may be done by use of ablation, that is, tissue destruction with cryosurgery or laser ablation, or by excision of tissue. Excisional modalities include laser conization, cold-knife conization, and electrosurgical loop excision (Loop Electrosurgical Excision Procedure). All treatment modalities, particularly excisional procedures, are suspected of increasing the risk of adverse future reproductive outcomes, such as preterm delivery and premature rupture of membranes (Wright, 2007b).

Evidence-based consensus guidelines for the management of women with biopsy-confirmed CIN have been developed and recently updated through the organizational efforts of the American Society for Colposcopy and Cervical Pathology (Wright, 2003, 2007a). In general, histologic CIN 1 can be observed indefinitely, especially in adolescents, or treated if it persists for at least 2 years. This is also the case for CIN 2 lesions in adolescents. However, CIN 2 in adult women and CIN 3 are treated by excision or ablation except in special circumstances. The "see and treat" approach in which loop excision is performed at initial colposcopy is an acceptable option for high-risk, adult patients who present with high-grade cytology and corresponding colposcopic abnormalities. A prospective study using this approach found that 84 percent of patients had CIN 2 or 3 within the excisional biopsy specimen (Numnum, 2005). In the case of unsatisfactory colposcopy and histologic CIN, a diagnostic excisional procedure is recommended to exclude the presence of occult high-grade CIN or invasive cancer.

Adenocarcinoma in situ (AIS) of the cervix, although uncommon, is increasing in incidence and typically diagnosed at a younger age (Krivak, 2001). Exclusion of invasive cancer and removal of all affected tissue remains the primary goal. Cold-knife conization is recommended to optimize specimen orientation, interpretation of histology, and preservation of margins (American College of Obstetricians and Gynecologists, 2005b). The risk of residual AIS is reported to be as high as 80 percent in patients with positive margins and therefore, repeat conization is advisable (Krivak, 2001). Even with negative conization specimen margins and endocervical curettage, there is risk of residual disease. Therefore, hysterectomy is recommended after childbearing is completed (Krivak, 2001; Poynor, 1995).

When colposcopic and histologic evaluation fail to reveal the presence of high-grade neoplasia, further surveillance is recommended based upon the original abnormal cytology result as listed in Table 29-9. Guidelines are available for the management of abnormal cytology and cervical neoplasia during pregnancy with treatment of persistent disease postpartum (Wright, 2007b).

Table 29-9 Surveillance of Abnormal Cervical Cytology in the Absence of Histologic High-Grade Neoplasia

Cytology	Colposcopy/Histology	Recommended Follow-Up
ASC-US, HPV status unknown	No CIN found	Repeat cytology at 12 months
ASC-US, HPV + or LSIL	No CIN found	Cytology at 6 and 12 months or HR HPV testing at 12 months
ASC-H	No CIN found	Cytology at 6 and 12 months or HR HPV testing at 12 months
HSIL	No CIN 2/CIN 3 found	Satisfactory colposcopy: review cytology and histology results and colposcopic findings or repeat colposcopy and cytology at 6 month intervals for 1 year or diagnostic excision; Unsatisfactory colposcopy: diagnostic excision
AGC	No CIN or glandular neoplasia	Repeat cytology at 6-month intervals for four times if HPV status unknown; If HPV negative, repeat cytology and HR HPV testing at 12 months; If HPV positive, repeat repeat cytology and HR HPV testing at 6 months
AGC, favor	No invasive carcinoma	Diagnostic excisional procedure

AIS	No invasive carcinoma	Diagnostic excisional procedure

AGC = atypical glandular cells; AIS = endocervical adenocarcinoma; ASC-H = atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; ASC-US = atypical squamous cells of undetermined significance; CIN = cervical intraepithelial neoplasia; HR HPV = high risk human papillomavirus; HSIL = high-grade squamous intraepithelial lesion; LSIL = low-grade squamous intraepithelial lesion.

Adapted from Wright, 2007b, with permission.

Modalities for the Treatment of Cervical Intraepithelial Neoplasia

Current treatment of CIN is limited to local ablative or excisional procedures. Whereas ablative procedures destroy cervical tissue, excisional methods provide histologic specimens that allow the evaluation of excision margins and assurance that invasive cancer is not present. Medical treatment using topical agents is currently investigational and not recognized as standard clinical practice. Selection of treatment modality depends on multiple factors including patient age, parity, desire for future fertility, size and severity of a lesion(s), contour of the cervix, prior treatment for CIN, and co-existing medical conditions such as immunocompromise. Most randomized clinical trials evaluating differences in treatment success are underpowered and no clear evidence shows any treatment technique to be superior (Martin-Hirsch, 2006; Mitchell, 1998). Most reports suggest surgical treatments have approximately a 90-percent success rate.

ABLATIVE TREATMENT MODALITIES

Before using ablative treatment modalities, there must be no indication of invasive cancer by cytologic or histologic evaluation or by colposcopic impression and no suspicion of glandular disease (Spitzer, 1998). Before ablative procedures, colposcopic examination should be deemed satisfactory, and cytologic and histologic results should be concordant. Ablative treatment modalities include cryosurgery, electrofulguration, and carbon dioxide (CO_2) laser.

Cryosurgery

Cryosurgery delivers a refrigerant gas, usually nitrous oxide, through flexible tubing to a metal probe which freezes tissue on contact (see Section 41-13, Treatment of Ectocervical Preinvasive Lesions). Cryonecrosis is achieved by crystallizing intracellular water. This treatment is appropriate for lesions associated with satisfactory colposcopic examination and with biopsy-proven squamous dysplasia limited to two quadrants of the cervix. Cryosurgery is generally not favored for the treatment of CIN 3 due to higher rates of disease persistence following treatment and lack of histologic specimen to exclude occult invasive cancer (Table 29-10) (Martin-Hirsch, 2006). Moreover, cryosurgery and other ablative techniques are not favored for HIV-positive women with CIN due to high failure rates.

Table 29-10 Cryosurgery: Clinical Characteristics

Advantages
Favorable safety profile
Outpatient procedure
No anesthetic requirements
Ease of procedure
Low-cost equipment with minimal maintenance
Bleeding complications rare
No proven adverse reproductive effects
Acceptable primary cure rate
Disadvantages
No tissue specimen for histopathology evaluation
Cannot treat lesions with unfavorable sizes or shapes
Uterine cramping
Potential for vasovagal reaction
Profuse vaginal discharge postprocedure
Cephalad migration of squamocolumnar junction

Adapted from Martin-Hirsch, 2006, with permission.

Carbon Dioxide Laser

Treatment with *l* ight *a* mplification by *s* timulated *e* mission of *r* adiation, or *laser,* is delivered using colposcopic guidance with a micromanipulator. This modality vaporizes tissue to a depth of 5 to 7 mm (see Section 41-13, Treatment of Ectocervical Preinvasive Lesions). Laser ablation is appropriate for biopsy-proven squamous intraepithelial lesions associated with a satisfactory colposcopic examination. The laser is well suited for large, irregularly shaped lesions of all grades.

EXCISIONAL TREATMENT MODALITIES

Lesions suspicious for invasive cancer and AIS of the cervix must undergo a diagnostic excisional procedure. In addition, excision is indicated for patients with unsatisfactory colposcopy with histologic CIN or unexplained high-grade or recurrent AGC cytology. It is also warranted in cases of cytologic versus biopsy discordance when histologic results are significantly less severe. Excision is recommended for any posttreatment recurrence of high-grade CIN to allow complete histologic evaluation of the specimen (Singer, 1994). Women with recurrent CIN have a higher risk for occult invasive cancer (Paraskevaidis, 1991). Excisional treatment modalities include loop electrosurgical excision procedure (LEEP), cold-knife conization (CKC), and laser conization.

Excisional and perhaps ablative procedures are associated with operative and long-term operative risks including cervical stenosis, cervical incompetence, plus preterm birth as described by Jakobsson (2007). Furthermore, Himes (2007) suggests women with a shorter conization-to-pregnancy interval, that is, less than two to three months are at particular increased risk for preterm birth.

Loop Electrosurgical Excision Procedure

This technique uses a thin wire on an insulated handle through which an electrical current is passed. This creates an instrument that simultaneously cuts and coagulates tissue under direct colposcopic visualization (see Section 41-13, Treatment of Ectocervical Preinvasive Lesions). Because LEEP can be performed using local anesthesia, it has become the primary outpatient treatment modality for high-grade cervical lesions including those that extend into the endocervical canal (Table 29-11). LEEP provides a tissue specimen with margins that can be histologically evaluated to assure complete lesion removal. Additionally, the size and shape of tissue excision can be customized by varying loop type and the sequential order in which loops are used. This helps conserve cervical stroma volume.

Table 29-11 Loop Electrosurgical Excision Procedure: Clinical Characteristics
Advantages
Favorable safety profile
Ease of procedure
Outpatient procedure using local anesthesia
Low costs of equipment
Tissue specimen for histopathology evaluation
Disadvantages
Thermal damage may obscure specimen margin status
Special training required
Risk of postprocedure bleeding
Theoretical risk of vapor plume inhalation

Cold-Knife Conization

This surgical procedure removes the entire cervical transformation zone including the cervical lesion by scalpel (see Section 41-14, Cervical Conization). It is performed in an operating room and requires general or regional anesthesia (Table 29-12). Cold-knife conization is preferred for cases of unsatisfactory colposcopy, particularly with high-grade CIN extending deep into the endocervical canal, with endocervical glandular disease, and with some posttreatment CIN recurrences. Patient selection favors those at highest risk for invasive cancer including cervical cytology suspicious for invasive cancer, patients older than 35 years with CIN 3 or CIS, large high-grade lesions, and biopsies showing AIS.

Table 29-12 Cold-Knife Conization Clinical Characteristics
Advantages
Anesthetized patient
Tissue specimen for histopathology without margin compromise
Enhanced patient support if hemorrhage is encountered
Variety of instruments to individualize conization
Disadvantages
Potential for hemorrhage
Lengthier procedure
Postoperative discomfort
General or regional anesthesia required
Operating room setting
High cost
Larger volume of cervical stroma removed
Increased risk of adverse reproductive outcomes

Carbon Dioxide Laser Conization

This method has the disadvantages of expense and some thermal compromise of margins, but the advantages of less blood loss and precise cone size and shape tailoring. Requiring special training, this procedure can be performed under local or general anesthesia.

Further Cytologic and Colposcopic Surveillance

Posttreatment, additional patient surveillance is required (Wright, 2007b). Patients with excision margins negative for CIN or who have undergone an ablative procedure may be followed with cytology testing alone or with colposcopy every 6 months until two negative evaluations are obtained before returning to routine screening. Alternatively, HPV DNA testing may be done between 6 and 12 months post-treatment, and colposcopy performed for persistent HPV infection as this is a sensitive marker of disease persistence. Cytology screening should continue for at least 20 years thereafter due to a persistently increased risk of cervical neoplasia after a diagnosis of high-grade CIN. If excision margins or endocervical curettage done immediately after an excision are positive for CIN 2 or CIN 3, surveillance with repeat cytology and endocervical sampling 4 to 6 months later is preferred but repeat excision is also acceptable. Repeat diagnostic excision is indicated for special circumstances such as AIS or microinvasive carcinoma at the excision margins.

Hysterectomy

Hysterectomy is unacceptable as primary therapy for CIN 1, 2 or 3 (Wright, 2007b). However, it may be considered when treating recurrent high-grade cervical disease if childbearing has been completed or when a repeat cervical excision is strongly indicated but technically not feasible. Although hysterectomy provides the lowest recurrence rate for CIN, invasive cancer must always be excluded beforehand. The choice of either a vaginal or abdominal approach is directed by other clinical factors. Hysterectomy is the

preferred treatment of AIS when future fertility is not desired.

Even with negative cervical margins, hysterectomy performed for CIN is not completely protective. Patients, particularly those who are immunosuppressed, are at risk for recurrent disease and require postoperative interval cytologic screening of the vaginal cuff (Saslow, 2002).

VAGINAL PREINVASIVE LESIONS

Incidence

Vaginal cancer is rare, with a U.S. 2005 incidence of less than 2 percent of all gynecologic cancers (National Cancer Institute, 2006). Approximately 90 percent of vaginal cancers are squamous and develop slowly from precancerous epithelial changes, similar to CIN, called vaginal intraepithelial neoplasia (VaIN).

Pathophysiology

Vaginal intraepithelial neoplasia (VaIN) has histopathology similar to CIN and VIN, is rarely found as a primary lesion, and most often develops as an extension of CIN, mainly in the upper third of the vagina (Diakomanolis, 2002; Hoffman, 1992a). Unlike the cervix, the vagina lacks an active transformation zone susceptible to HPV-induced neoplasia. However, HPV entry may result from vaginal mucosal abrasions and reparative metaplastic squamous cell activity (Woodruff, 1981).

Risk Factors

Although the natural history of VaIN is less understood than that of CIN, risk factors for VaIN are thought to be similar to those for CIN, suggesting similar etiology (see Table 29-2). This disease is primarily found in postmenopausal women with an average age of 64 years (range 36 to 85 years) (Hoffman, 1992b). However, with recent increases in HPV infection of the LGT being seen in a younger population, VaIN is now being diagnosed in younger women. Cervical or vulvar neoplasia increases the risk for VaIN and vaginal squamous cancer.

Diagnosis

Generally, VaIN is asymptomatic. If present, symptoms may include vaginal bleeding, discharge, and odor. Abnormal cytology is most often the first indication of VaIN, particularly if the patient lacks a cervix. Integral to management, subsequent colposcopic examination of the lower genital tract frequently locates a vaginal lesion for biopsy.

VAGINAL COLPOSCOPY

Because of redundant vaginal tissue, vaginal colposcopy can be cumbersome. A clear plastic speculum may aid visualization of all quadrants of the vagina, with tissue in the upper third of the vaginal vault requiring particular attention. By applying 3- to 5-percent acetic acid to vaginal mucosa, acetowhite changes consistent with neoplasia are identified. Half-strength Lugol solution applied to the vagina delineates nonstaining areas, which are likely to contain abnormal epithelium. Biopsy may be obtained by means of a biopsy forceps and an Emmett hook to elevate and stabilize vaginal tissue. Local anesthesia is usually needed for biopsies of the lower half of the vagina. Hemostasis is achieved using silver nitrate applicators or Monsel paste. Vaginal lesion size, location, and specific biopsy sites are carefully documented for future management and surveillance.

Treatment of VaIN

Like high-grade CIN, high-grade VaIN is believed to be a precancerous lesion and requires eradication (Punnonen, 1989; Rome, 2000). Because vaginal neoplasia is uncommon, most management strategies are derived from small, nonrandomized, retrospective, and statistically under-powered investigations. Management of VaIN depends on the grade of neoplasia and may include observation, excision, ablation, topical antineoplastics, or rarely, radiation therapy. Each treatment method has advantages and disadvantages and none has proven to be of superior efficacy. Management strategies are determined by colposcopic and histologic findings along with comprehensive patient counseling.

LOW-GRADE VAGINAL INTRAEPITHELIAL NEOPLASIA (VAIN 1)

In a long-term study following 132 patients with VaIN, Rome and colleagues (2000) found that an observational approach after

biopsy resulted in regression in 7 of 8 patients (88 percent) with VaIN 1. Furthermore, no VaIN 1 lesion progressed to high-grade VaIN or invasive cancer. This lesion most likely represents atrophy or transient HPV infection.

HIGH-GRADE VAGINAL INTRAEPITHELIAL NEOPLASIA (VAIN 2 AND 3)

The treatment modality choice for patients with high-grade VaIN is influenced by the location and number of lesions, whether the patient is sexually active, vaginal length, previous radiation therapy, previous treatment modalities in patients with recurrent VaIN, and clinician experience.

Excision

Wide local excision of a high-grade unifocal lesion or partial vaginectomy for multifocal lesions may be used. Hoffman (1992a) found that 9 of 32 patients (28 percent) with prior hysterectomy and VaIN 3 had occult invasive cancer in the vaginal cuff. Therefore, surgical excision should be considered for high-grade lesions involving the region of a posthysterectomy vaginal cuff scar.

Excisional procedures have the advantage of providing a surgical specimen for which resected margins can be examined and the presence of invasive vaginal cancer excluded. Moreover, partial vaginectomy has the highest cure rate and fewest recurrences for high-grade disease (Dodge, 2001). Wide local excision carries less morbidity than vaginectomy, but both modalities may be complicated by bladder or rectal injury and hemorrhage. Subsequent vaginal scarring and stenosis may compromise vaginal intercourse or cause dyspareunia.

As an alternative excisional modality, CO_2 laser causes significant thermal damage to the tissue specimen and is not recommended. Likewise, LEEP has poor depth control and carries a substantial risk of thermal damage to underlying pelvic structures, including the bladder and bowel.

Medical Ablation

Before medical treatment, as with other ablative procedures, the possibility of invasive cancer must be excluded. Persistent VaIN 1 or 2 and selected VaIN 3 lesions may be medically treated using 5-percent fluorouracil (5-FU) cream off-label, as it is not FDA approved for this indication (Efudex, Valeant Pharmaceutical International, Costa Mesa, CA). A 3-mL dose of cream is placed in the vaginal vault by plastic vaginal applicator every other day for 3 days during the first week of treatment and once weekly thereafter for up to 10 weeks. This cream is often associated with a robust inflammatory reaction that can include vaginal burning and vulvar irritation. Because of this, the cream is best placed at night. An occlusive, water-resistant ointment can be used to protect the vulva and introitus.

Patients selected for this treatment require thorough counseling, effective contraception as needed, consent for off-label medication use, and close monitoring. Surveillance should include vaginal cytology and colposcopy 2 months after treatment is completed.

Carbon Dioxide Laser Ablation

Laser ablation is well-suited for eradication of multifocal lesions and causes less scarring and blood loss than excisional modalities. Rarely, excessive bleeding and thermal damage to the bladder and bowel can occur.

Radiation Therapy

There is a role for radiation treatment of high-grade VaIN, but it carries significant morbidity and should be reserved for select cases. In a review of 136 cases of vaginal carcinoma in situ, radiation therapy was used in 27 patients, with a 100-percent cure rate noted. However, 63 percent developed significant complications that included vaginal stenosis, adhesions, ulceration, necrosis, and fistula formation (Benedet, 1984). Furthermore, radiation treatment compromises subsequent cytologic, colposcopic, and histologic interpretation. Disease recurrence often necessitates radical surgery.

Prognosis

In a study of 132 patients with high-grade VaIN, excision and CO_2 laser ablation had similar cure rates of 69 percent. Topical 5-flurouracil cream was curative in 46 percent of cases (Rome, 2000). Patients with any grade of vaginal neoplasia require long-term monitoring, as the recurrence rate for high-grade disease is significant.

VULVAR PREINVASIVE LESIONS

Incidence

Vulvar cancer is rare, with a U.S. 2006 incidence of less than 3 to 5 percent of all gynecologic cancers and less than 0.5 percent of all cancers in women (National Cancer Institute, 2006). Ninety percent of vulvar cancer is squamous and in some cases develops slowly through precancerous epithelial changes called vulvar intraepithelial neoplasia (VIN). However, VIN is not necessarily analogous to CIN, as the vulva lacks a transformation zone, and VIN does not progress to high-grade disease and cancer as often.

A recent study identifying trends in the incidence of vulvar carcinoma in situ found a 411 percent increase from 1973 to 2000. This trend is particularly pronounced in younger women and is thought to be linked to the increased incidence of sexually transmitted infections (Howe, 2001).

Pathophysiology

Although HPV DNA has been found in 72 percent of VIN lesions, HPV is less commonly associated with vulvar cancer, with most studies showing approximately 40-percent HPV DNA positivity (Madeleine, 1997; Monk, 1995). The progression of vulvar carcinoma in situ to invasive cancer has been strongly suggested, although not confirmed conclusively. Therefore, VIN 3 lesions are generally treated (van Seters, 2005).

ORIGINAL TERMINOLOGY

Terminology for squamous VIN was introduced by the International Society for the Study of Vulvar Disease (ISSVD) in 1986. Under this classification, VIN grades 1, 2, and 3 were defined by abnormal cellular changes found to varying thickness within the squamous epithelium as in the case of CIN (Wilkinson, 1986).

NEW MODIFIED TERMINOLOGY

Classification of VIN has recently been simplified by the ISSVD (Sideri, 2005). The older designation of VIN 1 has been eliminated, whereas VIN 2 and 3 categories have been combined. This redefinition reflects whether lesions are likely to be premalignant or not, and therefore whether or not lesions require therapy. The VIN 1 category has been eliminated because evidence is lacking that such lesions are cancer precursors. These lesions more likely represent benign reactive or HPV effect. The term VIN is now applied only to histologically high-grade squamous cell lesions and combines the previous categories of VIN 2 and 3 (Table 29-13).

Table 29-13 Vulvar Intraepithelial Neoplasia: Terminology and Characteristics

VIN Type	**Clinical Presentation and Risk Factors**
VIN, usual type	Formerly VIN 2, VIN 3, vulvar CIS
Warty	Younger women
Basaloid	Multicentric disease
Mixed	Oncogenic HPV infection
	Smoking, other STIs, immunosuppression
VIN, differentiated type	2â€"10% of former VIN 3 lesions Older, postmenopausal women Oncogenic HPV infection uncommon
VIN, unclassified type	Rare pagetoid lesions

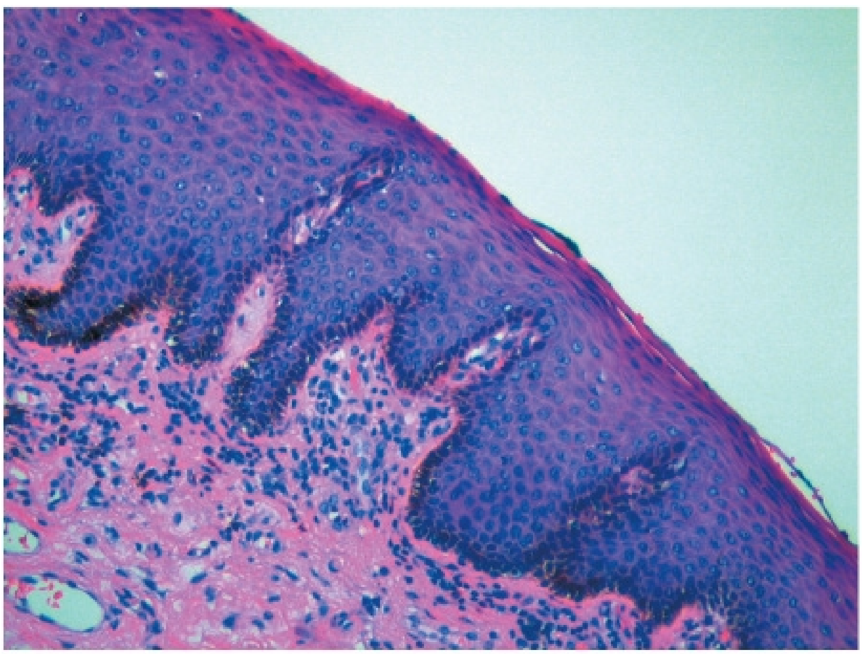
CIS = carcinoma in situ; HPV = human papillomavirus; STIs = sexually transmitted infections; VIN = vulvar intraepithelial neoplasia.

Vulvar intraepithelial neoplasia is now subcategorized into VIN, *usual type,* VIN, *differentiated type,* and VIN, *unclassified type.* Of these, VIN, usual type encompasses the former VIN 2 and 3 categories and clinically older dysplasia terms including carcinoma in situ. Lesions of VIN, usual type are associated with oncogenic HPV infection and can be grouped histologically as warty (condylomatous), basaloid, or mixed. In general, HPV DNA-positive high-grade VIN lesions morphologically resemble high-grade CIN and tend to be multifocal (Haefner, 1995).

The lower genital tract responds with a "field effect" to risk factors for cervical carcinoma, which may have similar influence on the squamous epithelia of the vulva and vagina (see Table 29-2). Accordingly, VIN, usual type is strongly associated with sexually transmissible infections and tobacco smoking, particularly in younger women (Hoffman, 1992b; Jones, 1994, 2005).

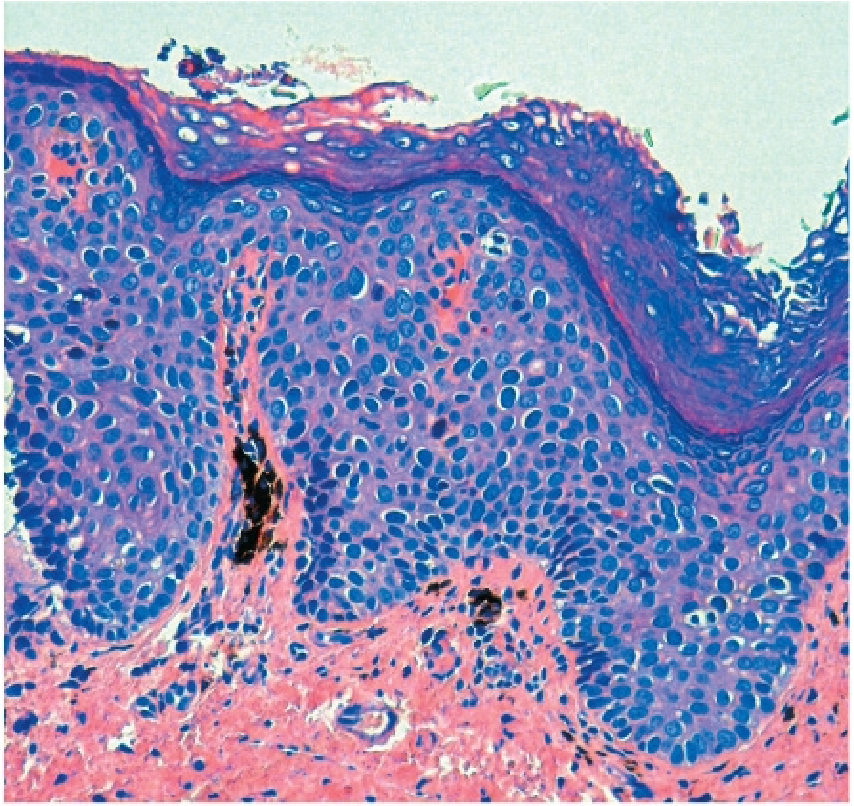
In contrast, VIN, differentiated type is less common and accounts for only 2 to 10 percent of all VIN 3 cases (Hart, 2001). This lesion is typically found in older, nonsmoking, postmenopausal women in their sixth and seventh decades. Infection with HPV is uncommon and probably does not play a role in the genesis of these lesions (Fig. 29-13).

FIGURE 29-13



A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

A. Normal vulvar histology. *(Courtesy of Dr. Raheela Ashfaq.)* **B.** VIN 3 histology. *(Courtesy of Dr. Raheela Ashfaq.)*

Rare pagetoid types of VIN 2 and 3 that cannot be classified in any of the above categories are termed VIN, unclassified type (Sideri, 2005).

Diagnosis

Vulvar intraepithelial neoplasia may be asymptomatic and discovered during routine gynecologic examination or during evaluation of abnormal cervical or vaginal cytology. When present, signs and symptoms may affect a patient's sexuality and quality of life (Table 29-14).

Table 29-14 Symptoms of Vulvar Intraepithelial Neoplasia
Pruritus
Pain or burning
Vulvar soreness
Bleeding
Discharge
Urination discomfort
Persistent ulcer
Skin area that has a different color or texture from surrounding tissue
Existing nevus change in symmetry or color
Lump or wart-like growth

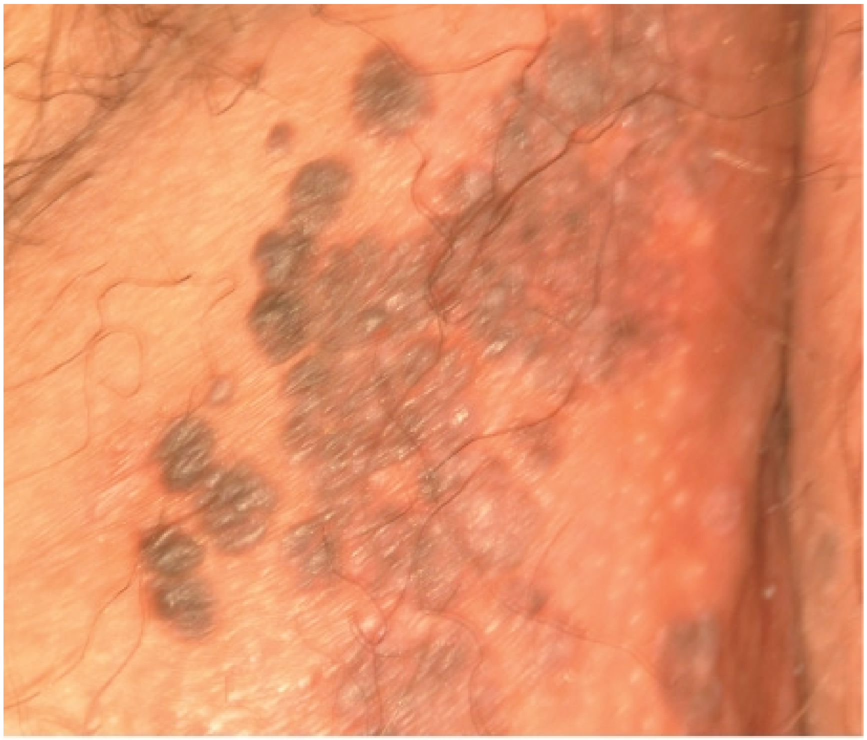
COLPOSCOPY

A histologic diagnosis is necessary before high-grade VIN is managed. This is best accomplished by magnification of the vulva and perianus, usually by use of a colposcope, or other means of simple magnification, with biopsy of the most abnormal-appearing areas.

Vulvar epithelial changes are enhanced by applying a 3- to 5-percent acetic acidâ€"soaked gauze pads to the vulva for 5 minutes prior to colposcopic examination. As an alternative, 1-percent toluidine blue may help define the best site for biopsy or the margins of surgical excision by staining abnormal nuclei (Joura, 1998). Procedurally, the vulva is painted with 1-percent toluidine blue, which is allowed to dry and then rinsed with 1-percent acetic acid. Toluidine blue is generally removed from normal tissue by the acetic acid rinse, whereas abnormal epithelium retains stain. Unfortunately, hyperkeratosis may give a false-negative result, and benign lesions or ulcers a false-positive test.

Vulvar intraepithelial neoplasia, usual type varies in clinical appearance. Some lesions are raised, hyperkeratotic, and pigmented (Fig. 29-14), whereas others are flat and white (Fig. 29-15). Often, lesions appear bulky, resemble condylomata, and are multifocal with extensive involvement of the perineum and adjacent skin.

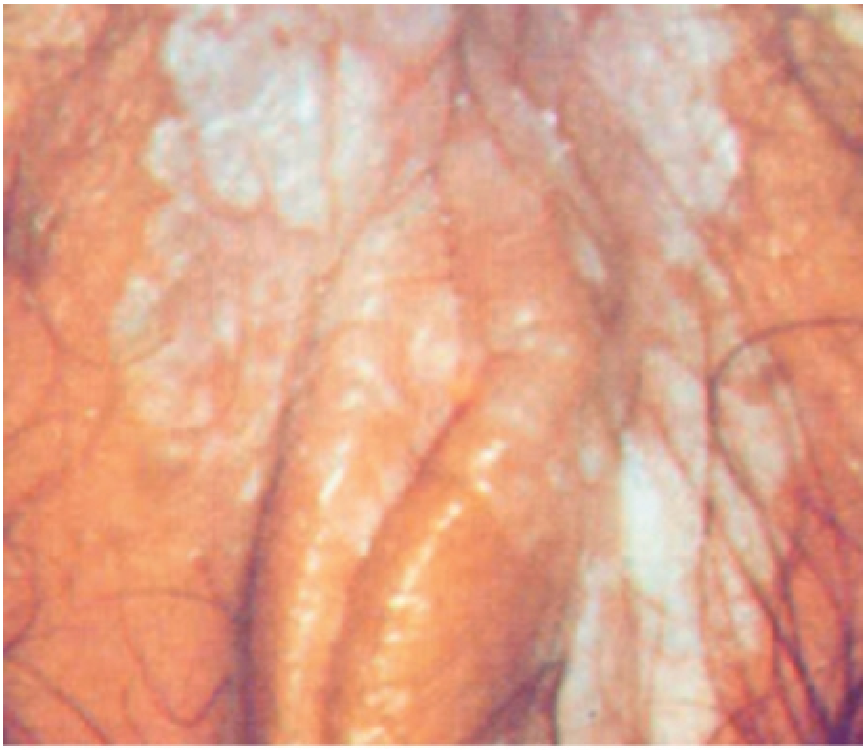
FIGURE 29-14



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Pigmented, multifocal, high-grade VIN.

FIGURE 29-15



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Multifocal leukoplakia typical of high-grade VIN.

Vulvar intraepithelial neoplasia, differentiated type is generally unifocal and associated with lichen sclerosus or vulvar hyperplasia. A lesion may appear as an ulcer, warty papule, or hyperkeratotic plaque. Any lesion suspicious for invasive carcinoma should be biopsied, particularly lesions that are slightly elevated, roughened, nodular, or ulcerated. This is especially true in older women.

Adequate biopsies can be obtained by using a local anesthetic and biopsy punch up to 6 mm diameter (see Chap. 4, Vulvar Biopsy). If lesions are close to the clitoral hood, a general anesthetic is often warranted. Careful documentation and mapping of vulvar area biopsy sites will aid management plans.

Management

VULVAR INTRAEPITHELIAL NEOPLASIA 1

As previously stated, the progression of VIN 1 to VIN 3 has not been established and the modified 2004 ISSVD terminology has eliminated the VIN 1 category entirely. Lesions reported as VIN 1 may be reassessed annually and generally resolve without treatment.

VULVAR INTRAEPITHELIAL NEOPLASIA 2 AND 3

Because high-grade VIN is relatively rare, there are no sufficiently powered, long-term, randomized controlled studies investigating its management. Regardless of the modality selected, treatment side effects are common and can include vulvar discomfort, poor wound healing, infection, and scarring that may result in chronic dyspareunia. Treatment objectives should include: (1) improving patient symptoms, (2) preserving the appearance and function of the vulva, and (3) excluding invasive disease.

Standard treatment of high-grade lesions of the vulva can be achieved by local destruction or excision. Medical management with topical immune modulators or systemic agents is currently investigational. Treatment of VIN 2 or 3 is individualized and based on lesion location, size, and clinician expertise. Many patients are best treated by combined excisional and ablative procedures.

Excisional Surgery

Extensive vulvar surgery for VIN is not always necessary if patients undergo close monitoring for disease progression or recurrence. Carcinoma in situ or large lesions in which invasive carcinoma cannot be excluded by simple biopsy are best managed by wide local excision (WLE) with a surgical margin that includes at least 5 mm of normal tissue (see Sections 41-15, Wide Local Excision of Vulvar Intraepithelial Neoplasia and 43-25, Skinning Vulvectomy). Because disease recurrence is related to surgical margin status, frozen section histology of the specimen margins should be evaluated intraoperatively (Friedrich, 1980; Jones, 2005). Hopkins (2001) reported disease recurrence rates of 20 percent and 40 percent for negative and positive surgical margins, respectively.

Wide local excision may require skin grafting and can be disfiguring. All vulvar surgeries require thorough preoperative counseling regarding expected anatomic results and sexual function.

Ablative Treatment

Although providing good cosmetic results, lesion ablation with CO_2 laser does not allow histologic evaluation of a surgical specimen. Therefore, the presence of invasive carcinoma must be excluded beforehand. Although generally less disfiguring than WLE, laser ablation can result in prolonged and painful healing and in prolonged wound discharge. Preoperative counseling regarding anticipated postoperative results mirrors that for WLE. Recurrence of VIN has been reported more commonly following laser vaporization than after WLE (Herod, 1996). However, Hoffman (1992b) reported that 15 of 18 patients (83 percent) with VIN 3 remained free of recurrent disease after CO_2 laser ablation.

Cavitational ultrasonic surgical aspiration (CUSA) may be used in the treatment of high-grade VIN confined solely to non-hair-bearing vulvar skin. Ultrasound is used to cause cavitation and disruption of affected tissue, which is then aspirated and collected (see Chap. 40, Cavitational Ultrasonic Surgical Aspiration). This technique provides the advantages of laser ablation with less scarring or pain and also provides a histologic specimen. However, the tissue specimen is severely fragmented during the process and lacks the diagnostic accuracy of surgically excised tissue for ruling out the presence of invasive cancer. Miller (2002) evaluated this procedure in 37 patients with VIN 2 or 3 and found an overall recurrence of 35 percent during a mean surveillance period of 33 months.

Involvement of the pilosebaceous units by VIN occurs in up to two thirds of cases, but rarely exceeds 2.5 mm in depth from the epidermal surface (Shatz, 1989). This is important for disease management, particularly if ablative procedures are considered.

Topical Treatment

Topical treatments are currently under investigation and have not yet become recommended clinical therapy. These agents include imiquimod 5-percent cream (Aldara, 3M, St. Paul, MN), cidofovir emulsion (Vistide, Gilead, Foster City, CA), and 5-percent fluorouracil cream.

Photodynamic therapy (PDT) using topical 5-aminolevulinic acid (5-ALA) has been used as tissue-conserving treatment for vulvar carcinoma in situ. Although PDT preserves tissue without scarring or disfigurement, it has a low response and high recurrence rate (Kurwa, 2000).

Prognosis and Prevention

There are accumulating case reports supporting the invasive potential of untreated, high-grade VIN (Jones, 2005). Jones reviewed the outcome of 113 patients with VIN 3 and found that seven of eight untreated patients progressed to vulvar cancer. In contrast, only 3.8 percent of treated patients progressed to invasive carcinoma (Jones, 1994). It is currently not possible to predict high-grade VIN lesion behavior. Regardless of the treatment modality chosen, recurrence is common, particularly in patients with multifocal disease and immunocompromise. Surveillance for persistent and recurrent LGT disease is advisable.

ANAL INTRAEPITHELIAL NEOPLASIA (AIN)

Incidence

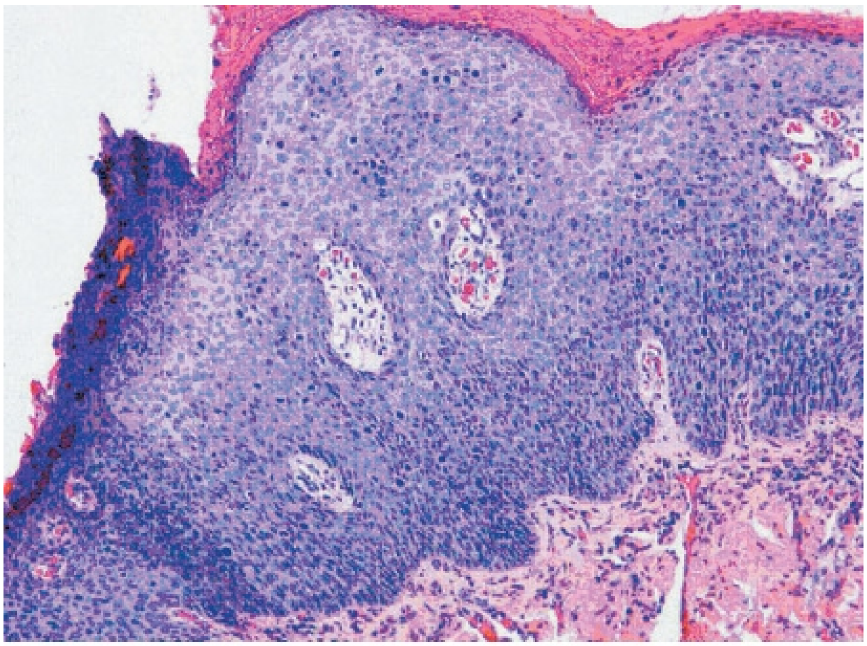
In the U.S., the incidence of anal cancer is increasing in both women and men (Melbye, 1994). Changes in sexual practices are likely partially responsible for this increase (Frisch, 1993). Anal cancer in women is strongly associated with sexually transmitted

infections including genital warts, infection with herpes simplex virus type 2, and infection with *Chlamydia trachomatis* (Daling, 1987).

Pathophysiology

As with cervical squamous cell cancers, oncogenic HPV types 16 and 18 are thought to be the principal etiologic agents responsible for the development of anal squamous cell cancers and their precursors (Zbar, 2002). Little is known of the natural history of anal HPV infection and its progressive potential in women, but it is suspected to behave similarly to cervicovaginal lesions. Cervical and anal lesions generally manifest adjacent to their respective squamocolumnar epithelial junctions, which in the anus is called the *transition zone* (Goldstone, 2001). Anal disease is classified by the same cytologic and histologic nomenclature used to describe cervical disease. Anal intraepithelial neoplasia (AIN) 1, 2, and 3 correspond to mild, moderate, and severe dysplasia, respectively (Fig. 29-16). Although not scientifically established, eradication of high-grade anal lesions may decrease the incidence of invasive cancer (Williams, 1994).

FIGURE 29-16



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

AIN 3 histology. *(Courtesy of Dr. Raheela Ashfaq.)*

Risk Factors

Risk factors for anal HPV lesions include anal receptive sexual activity, history of other sexually transmitted infections, immunosuppression, and tobacco smoking. Anal cancer and its likely precursor AIN 3 are increasing at higher rates in HIV-positive compared with HIV-negative patients (Frisch, 2000).

Diagnosis

SCREENING RECOMMENDATIONS

As with cervical cancer, prevention by screening persons at risk for abnormal anal cytology and treating high-grade anal lesions may be the best approach to decreasing the incidence of anal cancer (Berry, 2004; Friedlander, 2004; Palefsky, 1997). Specifically, some investigators believe annual anal cytology should be offered to all HIV-positive patients, but only if the infrastructure necessary to evaluate and manage abnormal cytology results and precancerous lesions is available (Palefsky, 2005; Panther,

2005). For the generalist who lacks adequate clinical resources and expertise to manage abnormal anal cytology, patients may be referred to tertiary care centers or colorectal surgeons for further evaluation and management. As a minimum, HIV-positive women with biopsy-proven LGT neoplasia should be provided a periodic digital examination of the anal canal.

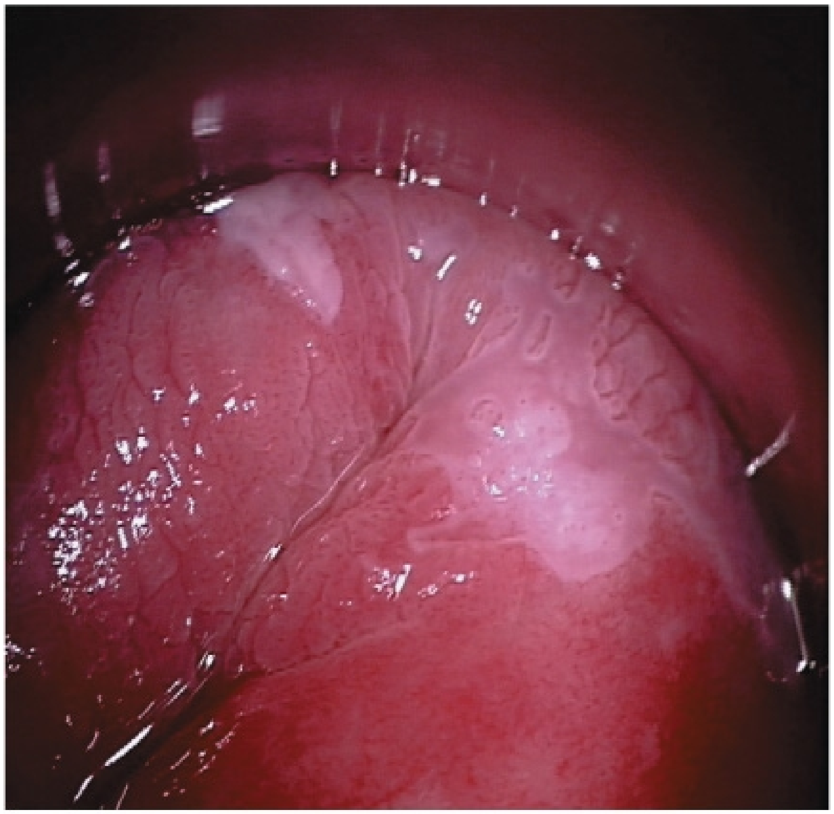
ANAL CYTOLOGY

Anal cytology using liquid-based preparations is more sensitive than that from conventional glass slides (Friedlander, 2004; Sherman, 1995). Sampling is obtained by inserting a water-moistened Dacron swab or endocervical brush approximately 5 cm into the anal canal above the anal transition zone and then withdrawing the sampling device with a circular motion while applying pressure to the anal canal wall. The swab is then either swirled in the cytology solution to release exfoliated cells or smeared on a glass slide and fixed with isopropyl alcohol. Nothing per rectum is recommended 24 hours prior to an anal cytology test. Anal cytology is currently reported using Bethesda 2001 terminology for cervical cytology.

Management

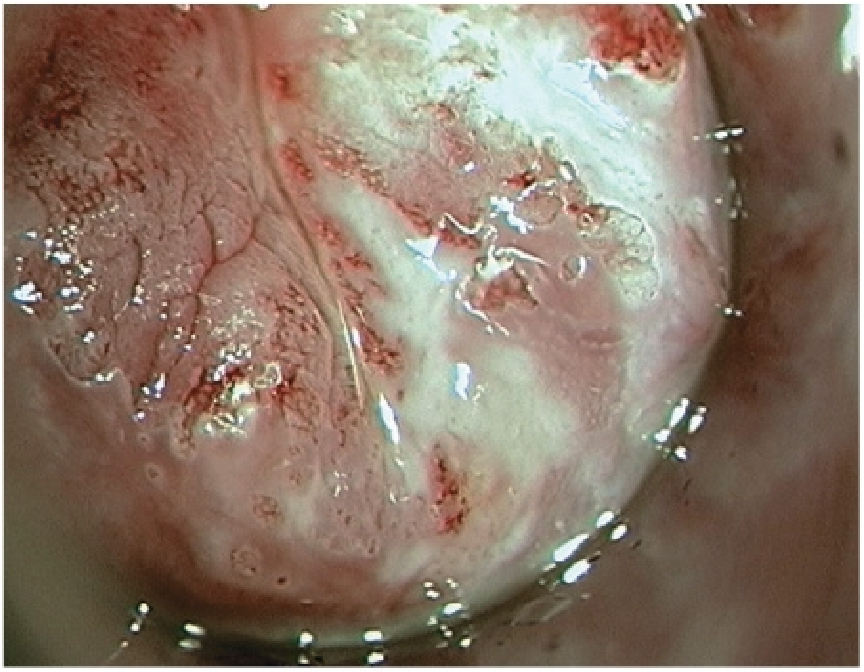
The natural history of AIN in not yet established and all abnormal cytology requires high resolution anoscopy (HRA) evaluation. Anoscopy is performed using technique and terminology similar to cervical colposcopy as described by Jay and colleagues (1997) (Fig. 29-17).

FIGURE 29-17



A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

A. AIN 1 acetowhite lesion. *(Courtesy of Naomi Jay, NP.)* **B.** AIN 3 acetowhite lesion. (*Courtesy of Naomi Jay, NP.)*

Treatment

Treatment is restricted to locally ablative or excisional procedures that eliminate individual high-grade intraepithelial lesions. Unlike the cervix, the entire anal squamocolumnar junction cannot be destroyed or removed. Treatment of biopsy proven high-grade AIN lesions can be accomplished by a variety of ablative procedures including the carbon dioxide laser or electrocautery performed under general anesthesia, or with infrared coagulation (IRC) as an office procedure (Chang, 2002; Goldstone, 2005). Cryosurgery and topically applied 85-percent trichloroacetic acid are alternative treatment methods. Excision is indicated in cases where invasive cancer is suspected by cytology or examination.

THE HIV-INFECTED PATIENT

Pathophysiology

Human immunodeficiency virus (HIV)-infected women are known to have a high burden of HPV-associated anogenital disease. Recent studies show that HIV-positive women have a higher prevalence and longer persistence of cervical HPV infection (Palekfsky, 2003).

Additionally, studies consistently suggest HIV-positive women have much higher rates of CIN compared with HIV-negative women (Ellerbrock, 2000; Wright, 1994). For example, in women infected with HIV, up to 60 percent of Pap smears exhibit cytologic abnormalities, and as many as 40 percent have colposcopic evidence of dysplasia.

HIV infection influences LGT disease progression. For example, early during the AIDS epidemic, Maiman and colleagues (1990) observed that all HIV-positive women with cervical cancer died as a result of their cervical cancer, compared with only 37 percent of HIV-negative women. Because of this and related studies, cervical cancer was designated as an AIDS-defining condition by the Centers for Disease Control and Prevention and remains so (Ahdieh, 2001; Brown, 1994; Centers for Disease Control and Prevention, 2002; Palefsky, 1999).

Management

SCREENING

Because of a significantly higher risk of developing LGT neoplasia, cervical cytologic screening should be obtained every 6 months for the first year after an HIV infection diagnosis (Byrne, 1989; Centers for Disease Control and Prevention, 2006). Thereafter, annual screening for life is recommended. In addition, women with HIV may benefit from routine anal cytology screening (Palefsky, 2001).

ABNORMAL CYTOLOGY

Any cervical cytologic abnormality was formerly an indication for colposcopic evaluation. However, revised guidelines recommend that cervical cytologic abnormalities in immunocompromised women be evaluated similarly to the general population (Wright, 2007a). HIV-positive women with cervical intraepithelial neoplasia are often found to have dysplastic epithelial disease throughout the LGT (Hillemanns, 1996). Therefore, any indication for colposcopy warrants thorough evaluation of the entire lower genital tract.

Treatment

TREATMENT SELECTION

Ablative therapy is not recommended for HIV-positive women with high-grade cervical disease. Excisional procedures including loop excision, carbon dioxide laser, and cold-knife conization provide histology specimens for margin evaluation and assurance that invasive cancer is not present. Although excisional therapy is effective for eradicating CIN in immunocompetent patients, the same treatment seems to be effective only in preventing progression to cancer in HIV-infected women (Heard, 2005). Moreover, persistence and recurrence rates for excised LGT disease are higher in women with HIV compared with those without HIV infection.

HIGHLY ACTIVE ANTI-RETROVIRAL THERAPY

The therapeutic impact of these drugs on HPV infection is poorly understood and conflicting results have been reported (Heard, 2004). To date, highly active anti-retroviral therapy (HAART) has not been shown to consistently improve the natural history of HPV-related diseases. Indeed, if HAART leads to increased longevity yet does not alter the incidence or progression of HPV-related disease, individuals on HAART may have sufficient time to develop HPV-related epithelial cancers (de Sanjose, 2002).

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CERVICAL CANCER: INTRODUCTION

Cervical cancer is the most common gynecologic cancer in women. Most of these cancers stem from infection with the human papillomavirus, although other host factors affect neoplastic progression following initial infection. Compared with other gynecologic malignancies, cervical cancer develops in a younger population of women. Thus, screening for this neoplasia with Pap smear sampling typically begins in adolescence or young adulthood.

Most early cancers are asymptomatic, whereas symptoms of advancing cervical cancer may include bleeding, watery discharge, and signs associated with venous, lymphatic, neural, or ureteral compression. Diagnosis of cervical cancer usually follows colposcopic examination and histologic evaluation of cervical biopsies.

This cancer is staged clinically, and stage is the most important indicator of long-term survival. Treatment varies and is typically dictated by this staging. In general, early stage disease is effectively eradicated surgically by either conization or radical hysterectomy. However, for those with advanced disease, chemoradiation is primarily selected. As expected, disease prognosis differs with tumor stage. Women with stage I disease typically have high survival and low recurrence rates, whereas those with advanced disease have a poorer long-term prognosis.

Prevention lies mainly in early detection. For this reason, regular Pap smear screening is recommended by the American College of Obstetricians and Gynecologists (2003) and by the U.S. Preventive Services Task Force (2003) (see Table 29-3).

INCIDENCE

Worldwide, cervical cancer is common, and ranks second among all malignancies for women (Parkin, 2005). In 2002, an estimated 493,000 new cases were identified globally and 274,000 deaths were recorded. In general, higher incidences are found in developing countries, and these countries contribute 83 percent of reported cases annually. Economically advantaged countries have significantly lower cervical cancer rates, and add only 3.6 percent of new cancers. This incidence disparity highlights successes achieved by cervical cancer screening programs in which Papanicolaou (Pap) smears are regularly obtained.

Within the United States, cervical cancer is the third most common gynecologic cancer and the sixth most common solid malignant neoplasm among women (Jemal, 2006). In the U.S., women have a 1 in 135 lifetime risk of developing this cancer. In 2006, the American Cancer Society estimated 9,710 new cases and 3,700 deaths from this malignancy (Parkin, 2005). Of U.S. women, African-Americans and women in lower socioeconomic groups have the highest age-standardized cervical cancer death rates from this cancer, and Hispanic and Latino women have the highest incidence rates (Table 30-1) (Jemal, 2006). This trend is thought to result mainly from financial and cultural characteristics affecting access to screening and treatment. The age at which cervical cancer develops is in general earlier than that of other gynecologic malignancies, and the median age at diagnosis ranges from 40 to 59 years. In women aged 20 to 39 years, cervical cancer is the second leading cause of cancer deaths.

Table 30-1 Cervical Cancer Age-Standardized Incidence and Death Rates						
	All Races	**White**	**African-American**	**Asian American and Pacific Islander**	**American Indian and Alaskan Native**	**Hispanic-Latino**
Incidence (%)	8.9	8.7	11.1	8.9	4.9	15.8
Death (%)	2.8	2.5	5.3	2.7	2.6	3.5

From Jemal, 2006, with permission.

RISKS

In addition to demographic risks, behavioral risks have also been linked with cervical malignancy. Most cervical cancers originate from cells infected with the human papillomavirus (HPV), which is sexually transmitted. Early coitarche, multiple sexual partners, and increased parity are associated with a substantially greater incidence of cervical cancer (see Table 29-2). In addition, smokers are at greater risk, although the mechanism underlying this risk in not known.

The greatest risk for cervical cancer is the lack of regular Pap smear screening. Most communities that have adopted such screening have documented decreased incidences of this cancer (Jemal, 2006).

Human Papillomavirus Infection

It is now widely accepted that HPV is the primary etiologic infectious agent, and a detailed discussion of this virus is found in Chapter 29, Human Papillomavirus (Ley, 1991; Schiffman, 1993). Although other sexually transmitted factors, including herpes simplex virus 2, may play a concurrent causative role, 95 percent of cervical cancers are associated with an oncogenic HPV subtype (Brinton, 1992). For example, in a population-based study of HPV infection and cervical neoplasia, 80 percent of high-grade squamous intraepithelial lesions (HSIL) and invasive lesions were associated with HPV infection (Herrero, 2000). Specifically in this study, one half of HSIL and invasive cervical cancer cases were attributable to HPV serotype 16. Serotype 18 was associated with 15 percent of invasive disease. Moreover, recent trials show that vaccination against HPV-16 and HPV-18 reduces incident and persistent infections with 92-percent and 100-percent efficacy, respectively. However, the effective duration of these vaccines is not yet known.

LOWER SOCIOECONOMIC PREDICTORS

Lower educational attainment, older age, obesity, smoking, and neighborhood poverty are independently related to lower rates of cervical cancer screening. Specifically, those living in impoverished neighborhoods have limited access to screening and may benefit from outreach programs that increase Pap smear screening availability (Datta, 2006).

CIGARETTE SMOKING

Both active and passive cigarette smoking increases the risk of cervical cancer. Among HPV-infected women, current and former smokers have a two- to threefold increased incidence of HSIL or invasive cancer. Passive smoking is also associated with increased risk, but to a lesser extent (Trimble, 2005). Of cervical cancer types, current smoking has been associated with a significantly increased rate of squamous cell carcinoma, but not of adenocarcinoma. Interestingly, squamous cell and adenocarcinomas of the cervix share most risk factors with this exception of smoking. Although the mechanism underlying the association between smoking and cervical cancer is unclear, smoking may alter HPV infection in those who smoke. For example, "ever smoking" has been associated with reduced clearance of high-risk HPV (Koshiol, 2006; Plummer, 2003).

Reproductive Behavior

Parity and combination oral contraceptive (COC) pill use has a significant association with cervical cancer. Pooled data from case-control studies indicate that high parity increases the risk of developing cervical cancer. Specifically, women with seven prior full-term pregnancies have an approximately fourfold risk, and those with one or two have a twofold risk compared with nulliparas

(Munoz, 2002).

In addition, long-term COC pill use may be a cofactor. There is a significant positive correlation between a low serum estradiol:progesterone ratio and shorter overall cervical cancer survival in premenopausal women (Hellberg, 2005). In vitro studies suggest that hormones might have a permissive effect for the growth of cervical cancer, by promoting cell proliferation and thus allowing cells to be vulnerable to mutations. In addition, estrogen acts as an anti-apoptotic agent permitting proliferation of cells infected with oncogenic HPV. In women who are positive for cervical HPV DNA and who use COCs, risks of cervical carcinoma increase by up to fourfold compared with women who are HPV-positive and never users of COCs (Moreno, 2002). Additionally, current COC users and women who are within 9 years of use have a significantly higher risk of developing both squamous cell and adenocarcinoma of the cervix (Berrington, 2007).

Sexual Activity

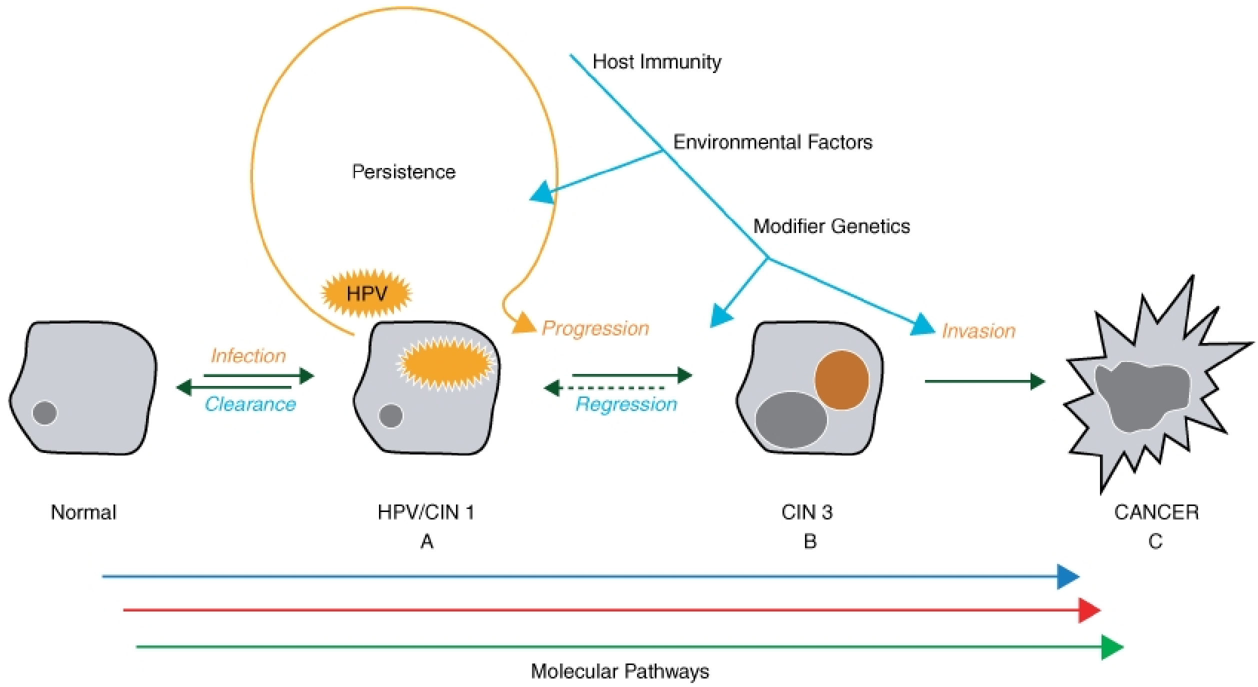
An increased number of sexual partners and early age of first intercourse have been shown to increase cervical cancer risks. Having more than six lifetime sexual partners imposes a significant increase in the relative risk of cervical cancer (Berrington, 2007). Similarly, early age of first intercourse before age 20 confers an increased risk of developing cervical cancer, whereas intercourse after age 21 only shows a trend towards an increased risk. Moreover, abstinence from sexual activity and barrier protection during sexual intercourse have been demonstrated to decrease cervical cancer incidence (Berrington, 2007).

PATHOPHYSIOLOGY

Tumorigenesis

Squamous cell carcinoma of the cervix typically arises at the squamocolumnar junction from a pre-existing dysplastic lesion, which in most cases follows infection with HPV (see Chap. 29, Outcome of HPV Infection) (Bosch, 2002). Although most women readily clear this virus, those with persistent infection may develop preinvasive dysplastic cervical disease (Fig. 30-1). In general, progression from dysplasia to invasive cancer requires several years, but wide variation exists. The molecular alterations involved with cervical carcinogenesis are complex and not fully understood. Uncovering these additional common molecular events has been difficult, and studies demonstrate vast heterogeneity. Accordingly, carcinogenesis is suspected to result from the interactive effects between environmental insults, host immunity, and somatic cell genomic variations (Helt, 2002; Jones, 1997, 2006; Wentzensen, 2004).

FIGURE 30-1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Diagram illustrating genesis of cervical cancers. There are two critical endpoints on the spectrum of cervical dysplasia. **A.** This initial point represents the cell at risk due to active HPV infection. **B.** The clinically relevant preinvasive lesion, cervical intraepithelial neoplasia 3 (CIN 3) or carcinoma in situ (CIS) represents an intermediate stage in cervical cancer development. **C.** Interactive effects between environmental insults, host immunity, and somatic cell genomic variations lead to invasive cervical cancer.

Human papillomavirus plays a major role in the development of cervical cancers. Also increasing evidence suggests that HPV oncoproteins may be a critical component of continued cancer cell proliferation (Mantovani, 1999; Munger, 2001). Unlike low-risk serotypes, oncogenic HPV serotypes can integrate into the human genome. As a result, with infection, oncogenic HPV's early replication proteins E1 and E2 enable the virus to replicate within cervical cells (see Fig. 29-3). These proteins are expressed in high levels early in HPV infection. They can lead to cytologic changes detected as low-grade squamous intraepithelial (LSIL) cytologic findings on Pap smears.

Amplification of viral replication and subsequent transformation of normal cells into tumor cells may follow (Mantovani, 1999). Specifically, viral gene products E6 and E7 oncoproteins are implicated in this transformation (Fig. 30-2). E7 protein binds to the retinoblastoma (Rb) tumor suppressor protein, whereas E6 binds to the p53 tumor suppressor protein. In both instances, binding leads to degradation of these suppressor proteins. The E6 effect of p53 degradation is well studied and linked with the proliferation and immortalization of cervical cells (Jones, 1997, 2006; Mantovani, 1999; Munger, 2001). Other mechanisms of genetic alterations and molecular changes that occur in precancerous and cancerous cervical cancer cells are outlined in Tables 30-2 and 30-3.

FIGURE 30-2

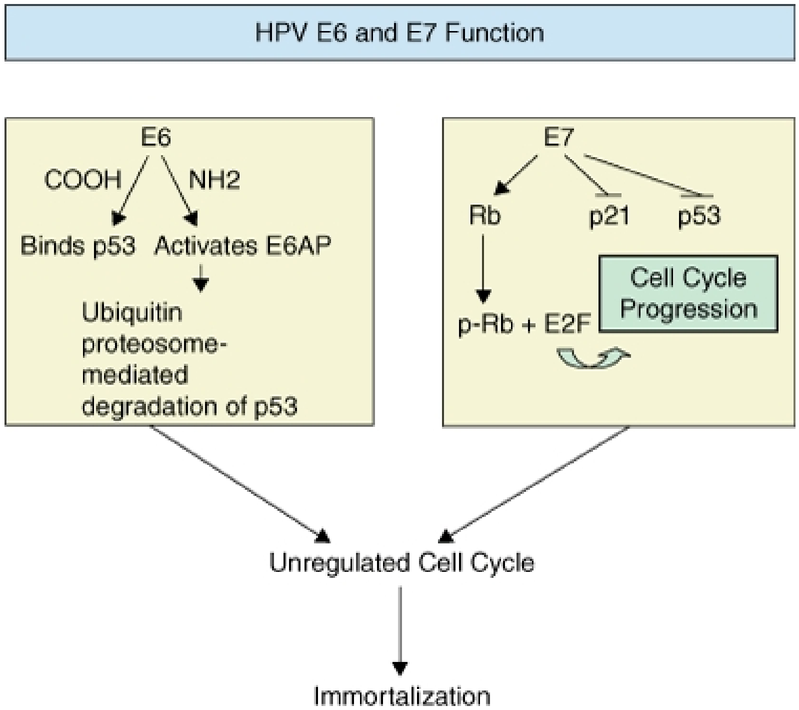


Diagram of E6 and E7 oncoproteins and p53, p21, and retinoblastoma (Rb) tumor suppressor proteins. On the left, viral oncoprotein E6 directly binds p53 and also activates E6AP to degrade p53 tumor suppressor protein. On the right, E7 oncoprotein phosphorylates retinoblastoma tumor suppressor protein resulting in release of E2F transcription factors, which are involved in cell cycle progression. E7 has also been shown to downregulate p21 tumor suppressor protein production and to subvert p53 function. The cumulative effect of oncoproteins E6 and E7 eventually result in cell cycle alteration, promoting uncontrolled cell proliferation.

Table 30-2 Genetic Alterations in Cervical Cancer

Genetic Alterations	**Mechanism**	**Function**
Overexpression of HPV E6 and E7 oncoproteins	Integration into host genome	Cell cycle deregulation; inhibition of apoptosis
Chromosomal aberrations	Regional gains and losses and global aneuploidy	Loss or gain of gene function
Epigenetic modification	Aberrant methylation	Loss of gene function

HPV = human papillomavirus.

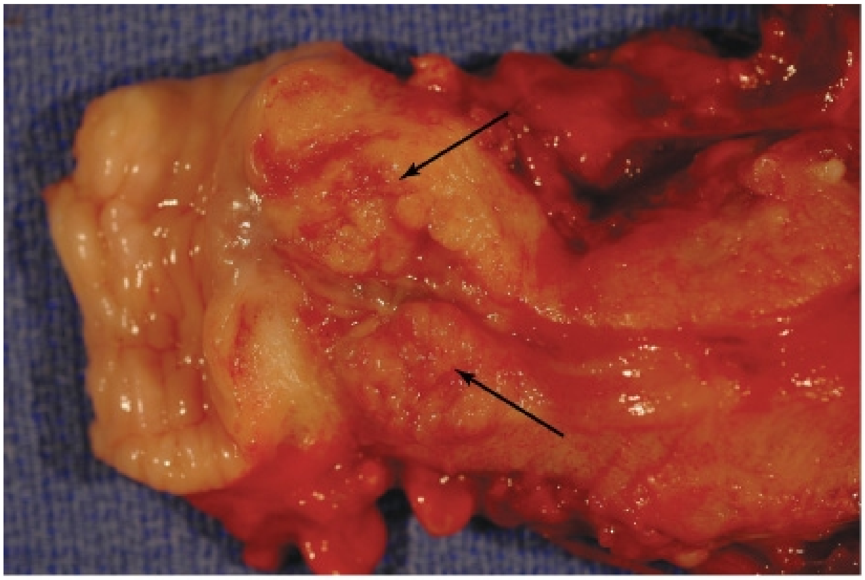
Table 30-3 Molecular Predictors in Cervical Cancer		
Molecular Predictor	**Function**	**Expression and Impact on Prognosis**
Cyclin D1	Cell cycle regulation	Decreased expression in CIN, increased expression in cancers
P16	Cell cycle regulation	Overexpressed in dysplasias and cervical cancers
PTEN	Candidate TSG	Epigenetic changes and loss of gene expression in cervical cancers Gene mutations indicative of advanced-stage disease
cIAP1	Suppression of apoptosis	Overexpression in cancer cells is an independent predictor of DFS
COX-2	Induces cyclooxygenase activity	Overexpressed in CIN 3 Overexpression in cancers associated with decreased overall survival
EGFR	Tyrosine kinase receptor	Overexpression is associated with lower DFS when associated with overexpression with COX-2
HLA	HLA*A201, HLA-B7, and DQB1*0302	Altered host immune response

cIAP1 = cellular inhibitor of apoptosis protein 1; CIN = cervical intraepithelial neoplasia; COX-2 = cyclooxygenase-2; DFS = disease-free survival; EGFR = epidermal growth factor receptor; HLA = human leukocyte antigen; PTEN = phosphatase and tensin homologue deleted on chromosome 10; TSG = tumor suppressor gene.

Tumor Spread

Following tumorigenesis, the pattern of local growth may be exophytic if a cancer arises from the ectocervix, or may be endophytic if it arises from the endocervical canal (Fig. 30-3). Lesions lower in the canal are more likely to be clinically visible during physical examination. Alternatively, growth may be infiltrative, and in these cases ulcerative lesions are common if necrosis accompanies this growth.

FIGURE 30-3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

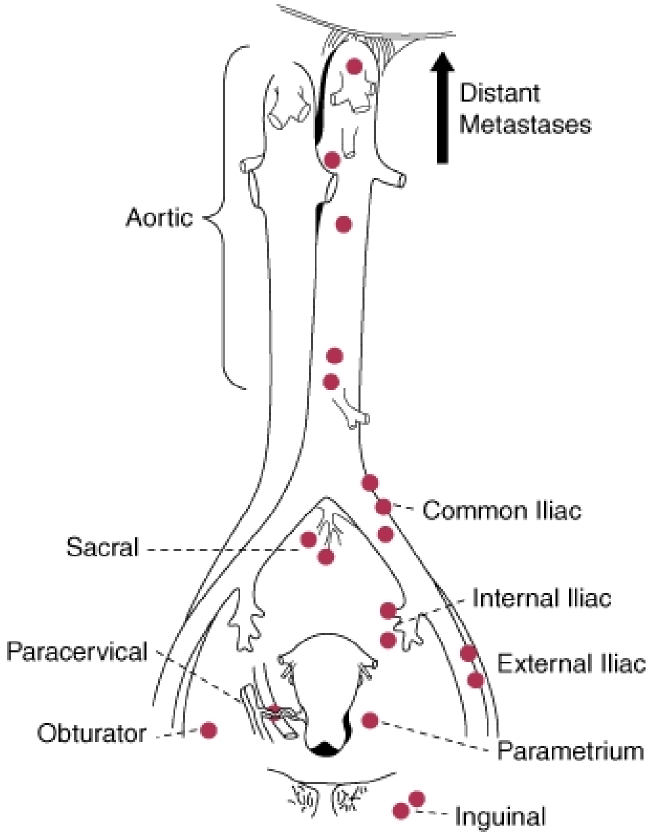
Photograph showing exophytic growth of cervical adenocarcinoma into the endocervical canal (**arrows**). *(Courtesy of Dr. John Schorge.)*

LYMPHATIC SPREAD

Lymph Node Groups

The cervix has a rich network of lymphatics, which follow the course of the uterine artery (Fig. 30-4). These channels drain principally into the paracervical and parametrial lymph nodes. Accordingly, these lymph nodes are clinically important and are removed as part of parametrial resection during radical hysterectomy. The lymphatics passing through the cardinal ligament empty into the ureteric node, which lies just lateral to the junction of the uterine artery. Although some experts consider this lymph node as distinct, others include this node within the paracervical nodal group.

FIGURE 30-4



Drawing of lymphatic drainage of the cervix. *(Redrawn from Henriksen, 1949, with permission.)*

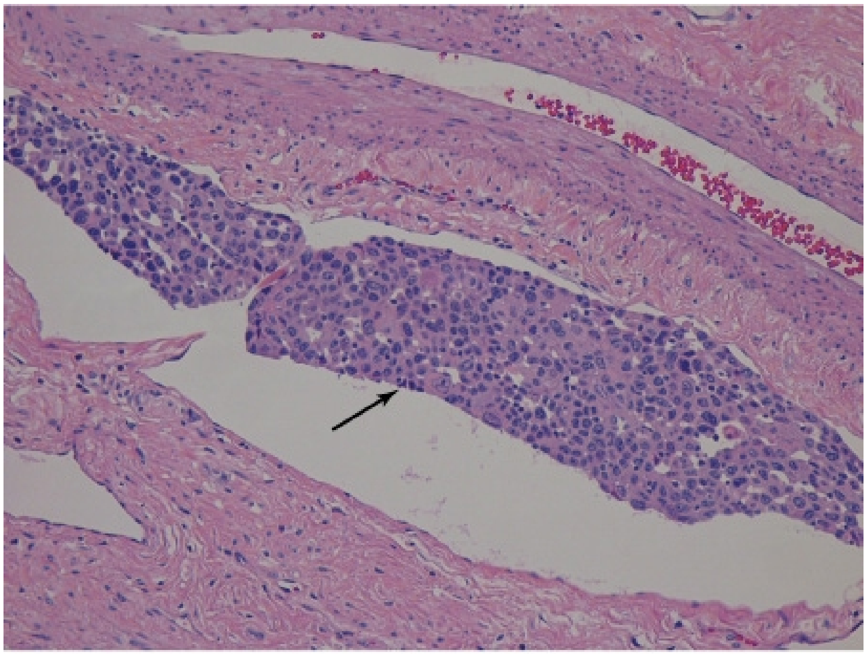
From the parametrial and paracervical nodes, lymph subsequently flows into the obturator lymph nodes and into the internal, external, and common iliac lymph nodes. In contrast, lymphatic channels from the posterior cervix course through the rectal pillars and the uterosacral ligaments to the rectal lymph nodes. These nodes are encountered during radical hysterectomy and removed with the uterosacral ligaments.

The pattern of tumor spread typically follows cervical lymphatic drainage. Thus, lymphatics involving the cardinal ligaments and anterior and posterior parametria are commonly involved. As primary lesions enlarge and lymphatic involvement progresses, local invasion increases and will eventually become extensive.

Lymphovascular Space Involvement

As tumor invades deeper into the stroma, it enters blood capillaries and lymphatic channels (Fig. 30-5). Termed *lymphovascular space involvement* (LVSI), this type of invasive growth is not included in the clinical staging of cervical cancer. However, its presence is regarded as a poor prognostic indicator, especially in early stage cervical cancers. Thus, the presence of LVSI often requires tailoring of the appropriate surgical procedure and adjuvant radiation treatment.

FIGURE 30-5



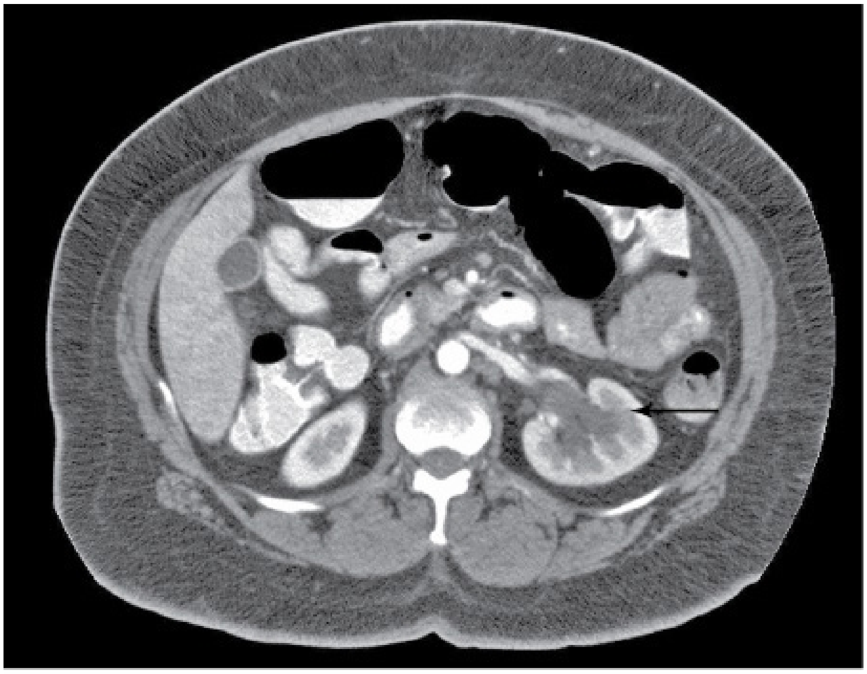
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photomicrograph of lymphovascular space involvement. A large lymphatic channel plugged with squamous cell carcinoma **(arrow)** . *(Courtesy of Dr. Raheela Ashfaq.)*

LOCAL TUMOR EXTENSION

With extension through the parametria to the pelvic sidewall, ureteral blockage frequently develops (Fig. 30-6). Additionally, the bladder may be invaded by direct tumor extension through the vesicouterine ligaments. The rectum is invaded less often because it is anatomically separated from cervix by the posterior cul-de-sac. Distant metastasis results from hematogenous dissemination, and the lungs, ovaries, liver, and bone are the most frequently affected organs.

FIGURE 30-6



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

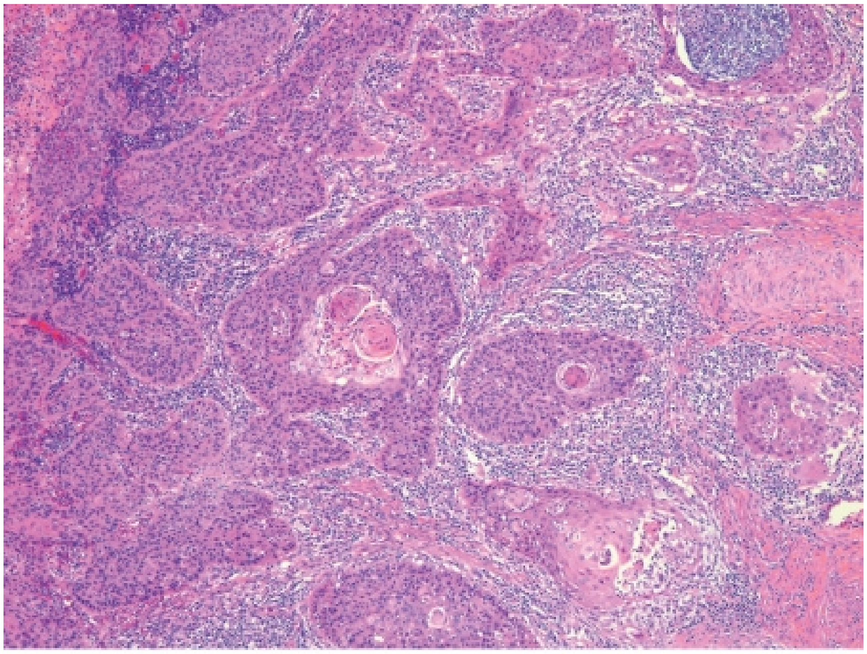
Computed tomography (CT) scan reveals hydronephrosis **(arrow)** caused by tumor compression of the right ureter. *(Courtesy of Dr. John Schorge.)*

HISTOLOGIC TYPES

Squamous Cell Carcinoma

The two most common histologic subtypes of cervical cancer are squamous cell and adenocarcinoma. Of these, squamous cell tumors predominate, comprise 85 percent of all cervical cancers, and arise from the ectocervix (Fig. 30-7). Over the past 30 years, there has been a decrease in the incidence of squamous cell cancers and an increase in the incidence of cervical adenocarcinomas. These changes may be attributed to an improved method of screening for early squamous lesions of the cervix and an increase in the prevalence of HPV (Vizcaino, 2000).

FIGURE 30-7



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photomicrograph of squamous cell cervical cancer. Nests of malignant cells invade the stroma accompanied by a brisk lymphocytic response. *(Courtesy of Dr. Raheela Ashfaq.)*

Evidence describing the prognosis of these two cell types is contradictory. For example, a randomized study of stage IB and IIA cervical cancer by Landoni and colleagues (1997) showed a statistically significant lower overall survival in those with adenocarcinoma compared with squamous cell carcinoma. However, the Gynecologic Oncology Group (GOG) in a subsequent study found that overall survival in women with stage IB squamous and adenocarcinomas of the cervix is similar (Look, 1996). Moreover, the 1998 International Federation of Obstetricians and Gynecologists (FIGO) annual report, which reported more than 10,000 squamous carcinomas and 1,138 adenocarcinomas, noted no difference in survival in stage I cancers. However, with advanced stage disease, evidence suggests that cervical adenocarcinomas (stage IIB to IVA) may portend a poorer overall survival risk compared with that of squamous cell carcinomas (Eifel, 1990; Lea, 2002).

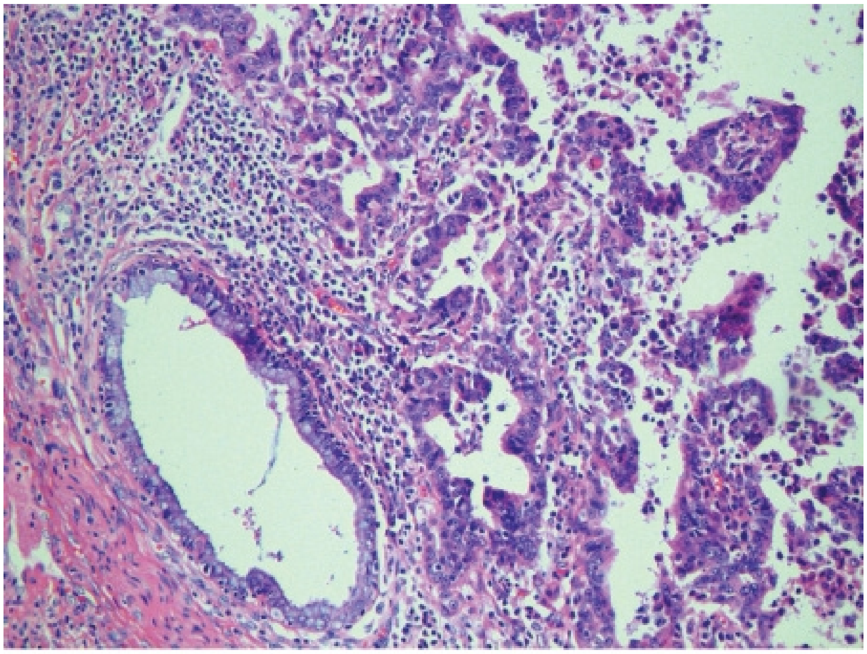
Adenocarcinomas

Adenocarcinomas are a group of cervical cancers comprised of the subtypes listed in Table 30-4. In contrast to squamous cell cervical carcinoma, adenocarcinomas comprise 10 to 15 percent of cervical cancers and arise from the endocervical mucus-producing glandular cells. Because of this origin within the endocervix, adenocarcinomas are often occult and may be advanced before becoming clinically evident.

Table 30-4 Histologic Subtypes of Cervical Cancer	
Squamous	
Adenocarcinoma	Endocervical type adenocarcinomas
	Endometrioid adenocarcinomas
	Minimal deviation adenocarcinoma
	Papillary villoglandular adenocarcinoma
	Serous adenocarcinoma
	Clear cell adenocarcinoma
	Mesonephric adenocarcinoma
Mixed cervical carcinomas	Adenosquamous carcinoma
	Glassy cell carcinoma
	Adenoid cystic carcinoma
	Adenoid basal epithelioma
Neuroendocrine tumors of the cervix	Large cell neuroendocrine
	Small cell carcinoma
Other malignant tumors	Sarcomas of the cervix
	Malignant lymphomas

Adenocarcinomas exhibit a variety of histologic patterns composed of diverse cell types. Of these, *mucinous endocervical adenocarcinomas* are the most common (Fig. 30-8). *Endometrioid adenocarcinomas* are the second most frequently identified and display glands resembling those of the endometrium. *Minimal deviation adenocarcinoma* is characterized by cytologically bland glands that are abnormal in size and shape. They contain an increased number of glands positioned at a deeper level than normal endocervical glands.

FIGURE 30-8



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photomicrograph of adenocarcinoma of the cervix. Note the surface growth of adenocarcinoma in relation to a normal endocervical gland. *(Courtesy of Dr. Raheela Ashfaq.)*

Mixed Cervical Carcinomas

These cervical malignancies are rare and histologically classified as adenosquamous, adenoid cystic, adenoid basal epithelioma, and glassy cell carcinoma. *Adenosquamous carcinomas* do not differ grossly from adenocarcinomas of the cervix. The squamous component is poorly differentiated and shows little keratinization. *Glassy cell carcinoma* describes a form of poorly differentiated adenocarcinoma in which cells display cytoplasm with a ground-glass appearance and a prominent nucleus with rounded nucleoli. *Adenoid cystic carcinoma* usually presents as a hard friable mass. Histologically this tumor resembles adenocarcinoma with adenocystic differentiation. Lastly, of this rare group of mixed tumors, *adenoid basal epitheliomas* typically behave in a benign fashion. Histologically, these tumors are characterized by nests and cords of small oval cells with a peripheral palisading arrangement.

Neuroendocrine Tumors of the Cervix

These malignancies include large cell and small cell tumors of the cervix. Large cell neuroendocrine tumors are highly aggressive and even early stage cancers have a relatively low disease-free survival rate despite treatment with radical hysterectomy and adjuvant chemotherapy (Albores-Saavedra, 1997). In contrast, small cell neuroendocrine carcinoma contains a uniform population of small cells with a high nuclear:cytoplasm ratio and resemble small cell carcinoma of the lung. Uncommonly, endocrine and paraendocrine tumors are associated with these neuroendocrine tumors.

Other Malignant Tumors

Rarely, the cervix may be the site of sarcomas and malignant lymphomas. Most of these tumors present as a bleeding cervical mass. Initially, differentiation of cervical sarcomas from primary uterine sarcoma requires careful pathologic examination and localization of the tumor's primary bulk. Cervical leiomyosarcomas and cervical stromal sarcomas have a poor prognosis, similar to uterine sarcomas (see Chap. 34, Leiomyosarcoma). Because these tumors are rare, statements regarding treatment of cervical

sarcomas are limited. Most cases are managed with multimodality treatment.

DIAGNOSIS

Symptoms

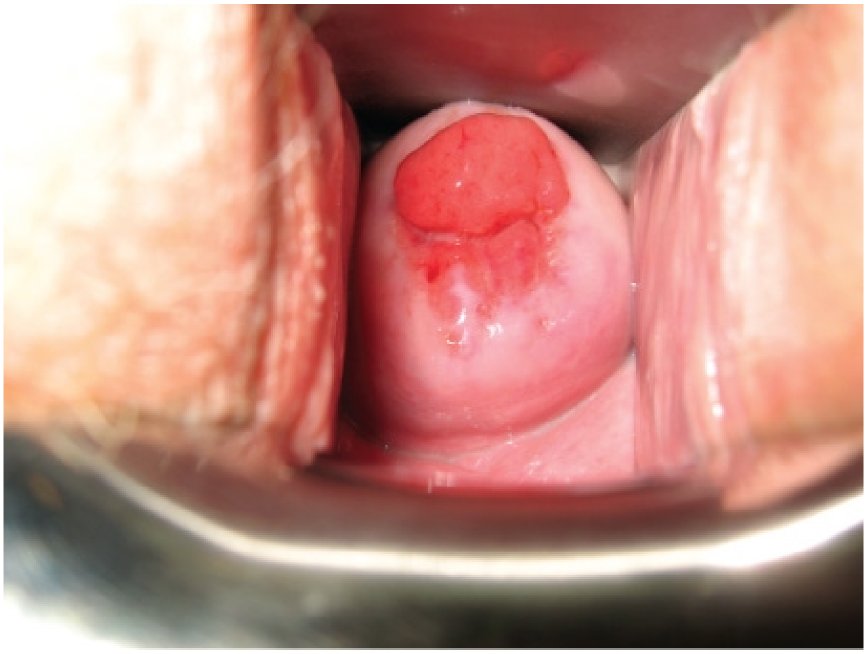
A large portion of women diagnosed with cervical cancer may be asymptomatic. For those with symptoms, however, early stage cervical cancer may create a watery, blood-tinged vaginal discharge. Intermittent vaginal bleeding that follows coitus or douching may also be noted. As a malignancy enlarges, bleeding typically intensifies and occasionally a woman may present to an emergency room with uncontrolled hemorrhage from a tumor bed. With parametrial invasion and extension to the pelvic sidewall, a tumor may compress adjacent organs to produce symptoms. For example, lower extremity edema and low back pain, often radiating down the posterior leg, may reflect compression of the sciatic nerve root, lymphatics, veins, or ureter by an expanding tumor. With ureteral obstruction, hydronephrosis and uremia can follow and may occasionally be initial presenting symptoms. Additionally, with tumor invasion into the bladder or rectum, women may note hematuria and/or symptoms of vesicovaginal or rectovaginal fistula.

Physical Examination

Most women with cervical cancer have normal general physical examination findings. However, with advancing disease, enlarged supraclavicular or inguinal lymphadenopathy, lower extremity edema, ascites, or decreased breath sounds with lung auscultation may indicate metastases.

In those with suspected cervical cancer, a thorough external genital and vaginal examination should be performed, looking for concomitant lesions. Human papillomavirus is a common risk factor for cervical, vaginal, and vulvar cancers. With speculum examination, the cervix may appear grossly normal if cancer is microinvasive. Visible disease displays varied appearances. Lesions may appear as exophytic or endophytic growth; as a polypoid mass, papillary tissue, or barrel-shaped cervix; as a cervical ulceration or granular mass; or as necrotic tissue (Fig. 30-9). A watery, purulent, or bloody discharge may also be present. For this reason, cervical cancer may mirror the appearance of different diseases. These include cervical leiomyoma, cervical polyp, prolapsing uterine sarcoma, vaginitis, cervical eversion, cervicitis, threatened abortion, placenta previa, cervical pregnancy, condyloma acuminata, herpetic ulcer, and chancre.

FIGURE 30-9



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photograph of invasive cervical cancer originating from the endocervix. *(Courtesy of Dr. David Miller.)*

During bimanual examination, a clinician may palpate an enlarged uterus resulting from tumor invasion and growth. Alternatively, hematometra or pyometra may expand the endometrial cavity following obstruction of fluid egress by a primary cervical cancer. Advanced cervical cancer cases may have vaginal involvement, and the extent of disease can be appreciated on rectovaginal examination. In such cases, palpation of the rectovaginal septum between the index and middle finger of an examiner's hand reveals a thick, hard, irregular septum. The proximal posterior vaginal wall is most commonly invaded. In addition, during digital rectal examination, parametrial, uterosacral, and pelvic sidewall involvement can be palpated. Either one or both parametria may be invaded and involved tissues feel thick, irregular, firm, and less mobile. A fixed mass indicates that tumor has probably extended to the pelvic sidewalls. However, a central lesion can become as large as 8 to 10 cm in diameter before reaching these sidewalls.

Papanicolaou Smear

Histologic evaluation of cervical biopsy is the primary tool used to diagnose cervical cancer. Although Papanicolaou (Pap) smears are performed extensively to screen for this cancer, this test does not always detect cervical cancer. Specifically, Pap smear testing has only a 55- to 80-percent sensitivity for detecting high-grade lesions on any given single test (Benoit, 1984; Soost, 1991). Thus, the preventive power of Pap smear testing lies in regular serial screening as outlined in Table 29-3. Moreover, in women who have stage I cervical cancer, only 30 to 50 percent of single cytologic smears obtained are read as positive for cancer (Benoit, 1984). Hence, the use of Pap smear alone for evaluation of suspicious lesions is discouraged. Importantly, these lesions should be directly biopsied with Tischler biopsy forceps or a Kevorkian curette (see Fig. 29-11).

Colposcopy and Cervical Biopsy

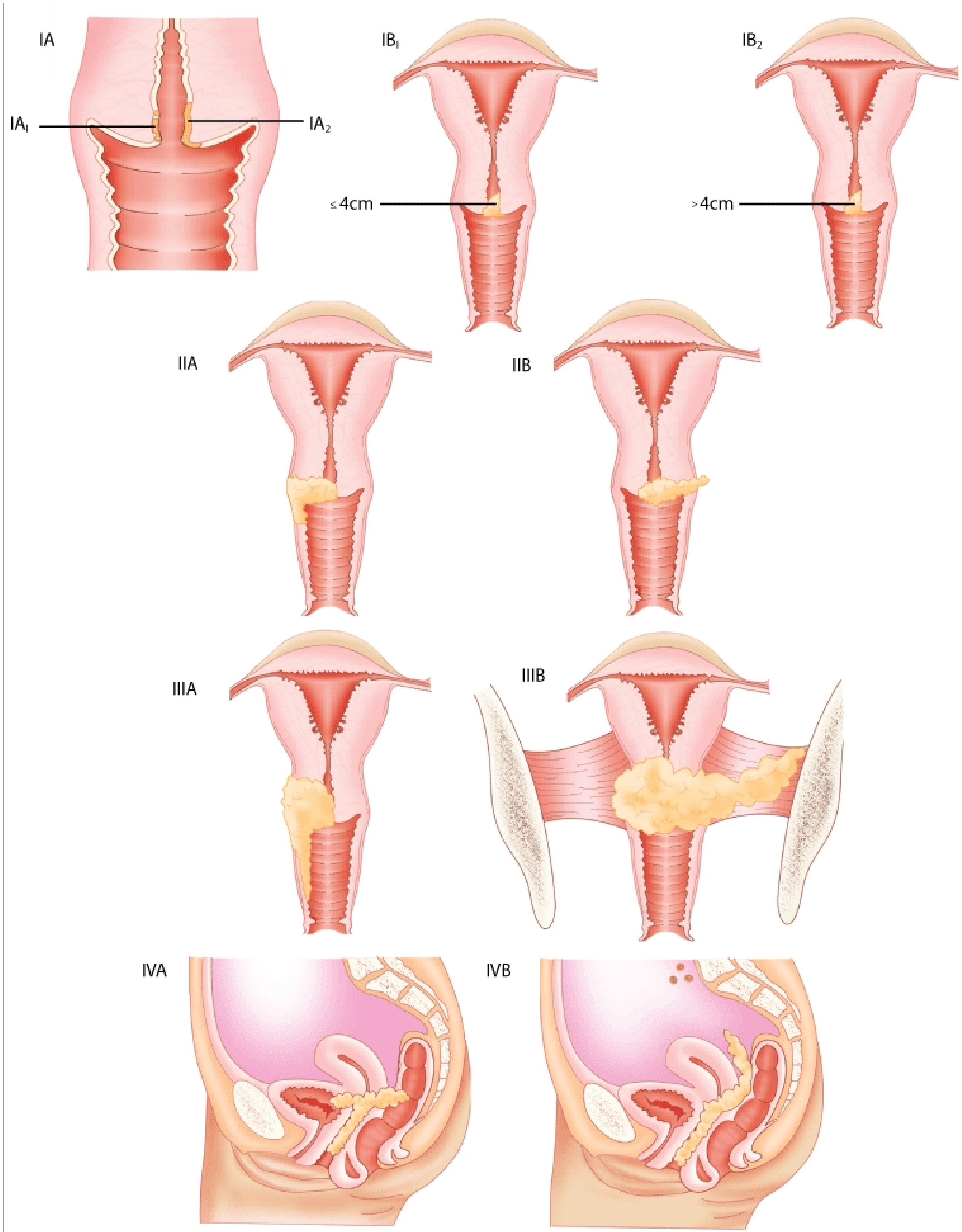
If abnormal Pap smear findings are noted, colposcopy is performed as described in Chapter 29, Colposcopy. During this evaluation, the entire transformation zone ideally is identified, and adequate cervical and endocervical biopsies are obtained. Cervical punch biopsies or conization specimens are the most accurate for allowing assessment of cervical cancer invasion. Both sample types typically contain underlying stroma and enable differentiation between invasive and in situ carcinomas. Of these, conization specimens provide a pathologist with a larger tissue sample and are most helpful in diagnosing in situ cancers and microinvasive cervical cancers.

STAGING

Clinical Staging

Cervical cancers are staged clinically, and interpretations are preferably confirmed with a bimanual pelvic examination under anesthesia (Table 30-5). The staging system widely used for cervical cancer is that developed by FIGO in collaboration with the World Health Organization (WHO) and the International Union Against Cancer (UICC) (Table 30-6 and Fig. 30-10). In this chapter, *early stage disease* refers to FIGO stages I through IIA. The term *advanced stage disease* describes stages IIB and higher.

FIGURE 30-10



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Drawing illustrates the FIGO stages of cervical cancer. *(From Quinn, 2006, with permission.)*

Table 30-5 Testing Used during Cervical Cancer Staging

Testing	**To Identify:**
Laboratory	
CBC	Anemia prior to surgery, chemotherapy, or radiotherapy
Urinalysis	Hematuria
Chemistry profile	
Liver function	Liver metastasis
Creatinine and BUN levels	Hydronephrosis
Radiologic	
Chest radiograph	Lung metastasis
Intravenous pyelogram (IVP)	Hydronephrosis
CT scan (abdomen and pelvis)	Lymph node metastasis, metastasis to other distant organs, and hydronephrosis
MR imaging	Local extracervical invasion + those for CT scan
PET scan	Lymph node metastasis
Procedural	
Cystoscopy	Tumor invasion into the bladder
Proctoscopy	Tumor invasion into the rectum
Examination under anesthesia	Extent of pelvic tumor spread

BUN = blood urea nitrogen; CBC = complete blood count; CT = computed tomography; MR = magnetic resonance; PET = positron emission tomography.

Table 30-6 Clinical Stages of Cervical Cancer (FIGO, Revised 1994)	
Stage	**Characteristics**
0	Carcinoma in situ, cervical intraepithelial lesion (CIN) 3
I	Carcinoma is strictly confined to cervix (extension to corpus should be disregarded)
IA	Invasion is limited to measured stromal invasion with a maximum depth of 5 mm and no wider than 7mm
IA1	Measured invasion of stroma no greater than 3 mm in depth and no wider than 7 mm
IA2	Measured invasion of stroma greater than 3 mm and no greater than 5 mm in depth and no wider than 7mm
IB	Clinical lesions confined to the cervix or preclinical lesions greater than IA
IB1	Clinical lesions no greater than 4 cm in size
IB2	Clinical lesions greater than 4 cm in size
II	Carcinoma extends beyond cervix but has not extended to pelvic wall; it involves vagina, but not as far as the lower third
IIA	No obvious parametrial involvement
IIB	Obvious parametrial involvement
III	Carcinoma has extended to the pelvic wall; on rectal examination there is no cancer-free space between tumor and pelvic wall; tumor involves lower third of vagina; all cases with hydronephrosis or nonfunctioning kidney should be included, unless they are known to be due to another cause
IIIA	No extension to pelvic wall, but involvement of lower third of vagina
IIIB	Extension to pelvic wall, or hydronephrosis or nonfunctioning kidney due to tumor
IV	Carcinoma has extended beyond true pelvis or has clinically involved mucosa of bladder or rectum
IVA	Spread of growth to adjacent pelvic organs
IVB	Spread to distant organs

FIGO = International Federation of Obstetricians and Gynecologists.

Modified from Quinn, 2006, with permission.

COMPUTED TOMOGRAPHY SCANNING

This is frequently used as a sole imaging study for identifying hydronephrosis, determining the extent of metastasis, and treatment planning. Specifically, computed tomography (CT) scanning has been most valuable in evaluation of para-aortic lymph nodes. For these nodes, CT scanning has a specificity of 100 percent and a sensitivity of 67 percent. However, for pelvic nodes, its sensitivity of 25 percent is substantially lower (Camilien, 1988). Alternatively, lymphangiography may be performed and has 79-percent sensitivity and 73-percent specificity. Its use, however, for cervical cancer staging is uncommon (Heller, 1990).

MAGNETIC RESONANCE IMAGING

This radiologic tool may also aid clinical staging, primarily by determining extracervical extension. In this role, magnetic resonance (MR) imaging is accurate in localizing cervical tumors, excluding parametrial invasion, and confirming myometrial and internal cervical os invasion (Sahdev, 2007). Moreover, for para-aortic nodal metastasis, MR imaging offers sensitivity comparable with CT scanning.

POSITRON EMISSION TOMOGRAPHY

This nuclear medicine study uses radioisotope tagged substrates such as glucose (2-[18F]-fluoro-2-deoxy-D glucose [FDG]) and creates images based on substrate metabolism within the body. In detecting para-aortic nodal metastasis in women with cervical cancer, preliminary experience has shown a cumulative sensitivity of 78 percent (Lin, 2003; Narayan, 2001; Rose, 1999a; Yeh, 2002). Moreover, positron emission tomography (PET) scanning may allow improved prediction of clinical outcome compared with CT scanning. For example, Grigsby and colleagues showed that the survival rate after pelvic radiation therapy for patients with FDG para-aortic nodal uptake (PET+) and with normal para-aortic anatomy identified by CT scanning was identical to that of patients with PET+ and abnormal para-aortic nodes by CT scanning (Grigsby, 2001).

Surgical Staging

LYMPH NODE DISSECTION

Surgical evaluation of retroperitoneal lymph nodes offers accurate detection of pelvic and para-aortic metastasis. In addition, debulking of tumor-laden nodes is also achieved. As a result, lymph node dissection may enhance management of and improve survival rates in patients with advanced stage cervical cancer.

During this dissection, most experts recommend lymph node biopsy in the common iliac and para-aortic region and selective biopsy of macroscopic lymph nodes (Querleu, 2000). Traditional laparotomic transperitoneal and extraperitoneal as well as laparoscopic approaches to these procedures have been studied. Although diagnostically equivalent, laparoscopic approaches offer the postoperative advantages of laparoscopic surgery. In addition, laparoscopic node dissection has been associated with significantly less radiation morbidity than radiation following laparotomic approaches (Vasilev, 1995).

One advantage to surgical staging is its improved sensitivity to detect pelvic and para-aortic nodal metastasis more accurately than radiologic techniques (Goff, 1999). Surgical staging enables the detection of microscopic metastasis and confirms macroscopic nodal metastasis. Moreover, for those with locally advanced cervical cancer, surgical staging can be performed with acceptable morbidity, and findings may modify a patient's primary treatment strategy based on the level of nodal metastasis. Retrospective studies have suggested a statistically significant survival benefit to extended chemotherapy and/or extended field radiation therapy if positive pelvic/para-aortic nodes are identified (Hacker, 1995; Holcomb, 1999).

In addition to its diagnostic power, surgical staging also permits debulking of grossly positive nodes. As a result, radiation fields during radiotherapy may be modified and lead to fewer radiotherapy complications.

However, evidence supporting a survival benefit from de-bulking macroscopic para-aortic nodes is contradictory. Although some retrospective studies have shown that disease-free survival rates for patients whose macroscopic nodal disease has been resected is similar to that of women with microscopic nodal disease, this benefit does not extend to overall survival rates (Cosin, 1998; Hacker, 1995).

Despite these suggested benefits, some experts argue that the benefits of surgical staging, if any, are minimal. These studies estimate only a 4- to 6-percent survival benefit after aggressive surgical debulking of retroperitoneal lymph nodes (Kupets, 2002; Petereit, 1998).

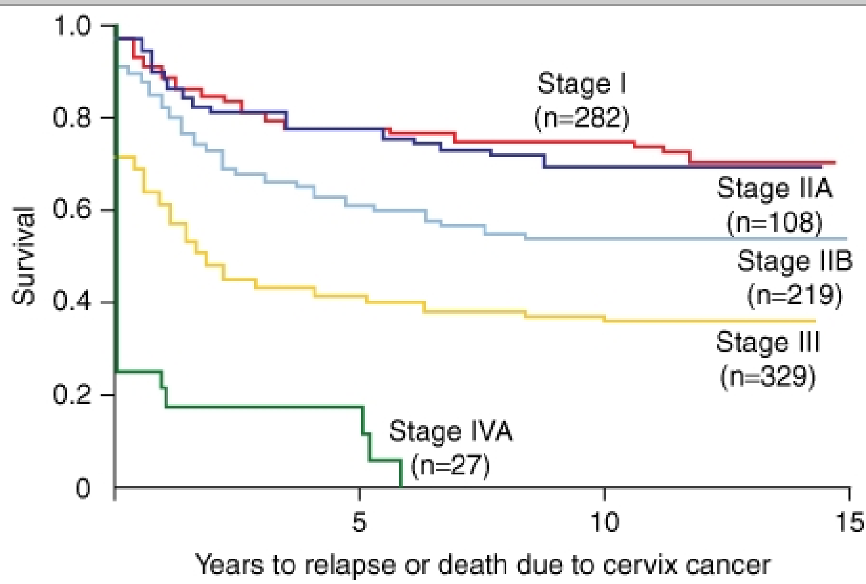
Prognosis

PROGNOSTIC FACTORS

The significance of tumor burden on survival has been well demonstrated, whether measured by FIGO stage, centimeter size, or surgical staging (Stehman, 1991). Of these definers, FIGO stage is the most significant prognostic factor (Fig. 30-11 and Table 30-

7). However, within each stage distribution, lymph node involvement also becomes an important factor in determining prognosis. For example, in early stage cervical cancer (stages I through IIA), nodal metastases are an independent predictor of survival (Delgado, 1990; Tinga, 1990). A GOG study demonstrated an 86-percent, 3-year survival for women with early stage cervical cancer and negative pelvic lymph nodes, compared with a 74-percent similar survival in patients who had one or more positive lymph nodes (Delgado, 1990).

FIGURE 30-11



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Graph illustrates decreased 5-year survival with advancing FIGO stage. *(From Fyles, 1995, with permission.)*

Table 30-7 Cervical Cancer Survival Rates According to Stage

Stage	5-Year Survival
IA	100%
IB	88%
IIA	68%
IIB	44%
III	18â€"39%
IVA	18â€"34%

Compiled from Grigsby, 1991, Komaki, 1995, and Webb, 1980, with permission.

In addition, the number of nodal metastases is also predictive. Retrospective studies have demonstrated significantly higher 5-year survival rates in those with one positive lymph node compared with women with multiple involved nodes (Tinga, 1990). Similarly, the negative prognostic impact of lymph node involvement in advanced stage (stage IIB through IV) cervical cancer has been demonstrated by several authors. In general, microscopic nodal involvement has a better prognosis than macroscopic nodal disease (Cosin, 1998; Hacker, 1995).

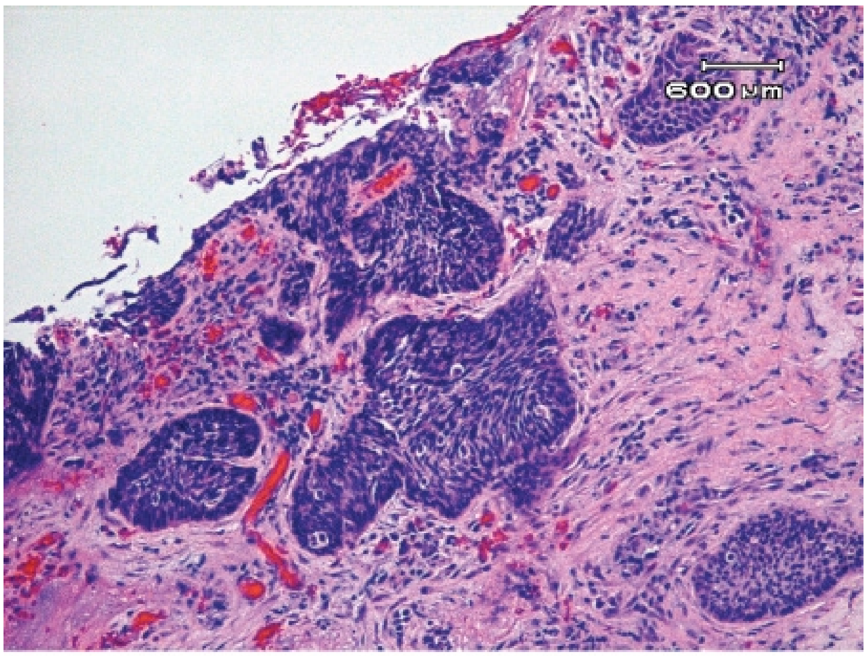
TREATMENT

Primary Disease

STAGE IA

The term *microinvasive cervical cancer* identifies this subgroup of small tumors. Specifically, as seen in Table 30-6, criteria for stage IA tumors limits invasion depth to no greater than 5 mm and lateral spread to no wider than 7 mm (Fig. 30-12). Microinvasive cervical cancer carries a minor risk of lymph node involvement and excellent prognosis following treatment. A retrospective study compared tumors with horizontal spread less than or equal to 7 mm and those with greater than 7 mm spread. Higher rates of pelvic lymph node metastasis and recurrence rates were noted as tumor spread further than 7 mm (Takeshima, 1999).

FIGURE 30-12



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photomicrograph of microinvasive squamous cell cervical cancer. Microinvasive squamous cell carcinomas are not grossly visible and are identified microscopically. These foci are not to exceed 5 mm in depth or 7 mm in lateral spread. *(Courtesy of Dr. Raheela Ashfaq.)*

Stage IA tumors are further divided into IA1 and IA2. These cancers are subdivided to reflect increasing depth and width of invasion and increasing risks for lymph node involvement (see Table 30-6).

Stage IA1

These tumors invade no deeper than 3 mm, spread no wider than 7 mm, and are associated with the lowest risk for lymph node involvement. Squamous cervical cancers with stromal invasion less than 1 mm have a 1-percent risk of nodal metastasis, and those with 1 to 3 mm of stromal invasion carry a 1.5-percent risk. Of 4,098 women studied with this tumor stage, less than 1 percent died of disease (Ostor, 1995). Such evidence supports conservative management of stage IA1 squamous cell cancer if lymphovascular space invasion (LVSI) is absent. These lesions may be effectively treated with cervical conization alone (Keighley, 1968; Kolstad, 1989; Morris, 1993; Ostor, 1994). However, a total intrafascial hysterectomy (type I hysterectomy) via an abdominal, vaginal, or laparoscopic approach is preferred for women who have completed childbearing.

The presence of LVSI in stage IA1 microinvasive cancers increases the risk of lymph node metastasis and cancer recurrence to approximately 5 percent. Accordingly, at our institution, these cases are traditionally managed with modified radical hysterectomy (type II hysterectomy) and pelvic lymphadenectomy.

Adenocarcinomas are typically diagnosed at a more advanced stage than squamous cell cervical cancers. Thus, microinvasive adenocarcinomas present a unique management dilemma, due to sparse data regarding this tumor stage. However, based on evaluation of Surveillance Epidemiology and End Result (SEER) data provided by the National Cancer Institute, the incidence of lymph node involvement is similar to that of squamous cancers (Smith, 2002). Of microinvasive cervical adenocarcinomas, 21 cases managed with uterine preservation and conization have been reported in the literature (Andersen, 2002; Schorge, 2000). Of these cases, no recurrences were identified following brief surveillance.

Stage IA2

Cervical lesions with 3 to 5 mm of stromal invasion have a 7-percent risk of lymph node metastasis and a greater than 4-percent risk of disease recurrence. In this group of women, the safety of conservative therapy is yet to be proven. Thus, for this degree of microinvasion modified radical hysterectomy and pelvic lymphadenectomy is warranted.

A few authors have reported management of stage IA2 squamous cervical lesions with radical trachelectomy and lymphadenectomy for fertility preservation. Several studies have also recommended that a nonabsorbable cerclage be placed concurrently with such radical trachelectomy to improve cervical competence during pregnancy. These procedures have high cure rates and successful pregnancies have been reported. If women are carefully selected for younger age, lower body mass index (BMI), smaller tumor size (<2 cm), and negative nodal involvement, then reported recurrence rates are similar to those of radical hysterectomy (Burnett, 2003; Covens, 1999a, 1999b). Preoperative MR imaging is recommended in these cases. If tumor has extended past the internal cervical os, then trachelectomy is contraindicated. Although this technique is promising, it carries a learning curve, and further studies to validate its efficacy are needed.

Alternatively, patients with microinvasive carcinoma (stages IA1 and IA2) can be treated with intracavitary brachytherapy alone with excellent results (Grigsby, 1991; Hamberger, 1978). Potential candidates for vaginal brachytherapy include women who are elderly, are not surgical candidates due to other concurrent medical disease, or do not wish to preserve ovarian or sexual function.

RADICAL HYSTERECTOMY

Women with FIGO stage IA2 through IIA cervical cancer may be selected for radical hysterectomy. In addition, surgery is appropriate for those who are physically able to tolerate an aggressive surgical procedure, those who wish to avoid the long-term effects of radiation therapy, and/or those who have contraindications to pelvic radiotherapy. Typical candidates include young patients who desire ovarian preservation and retention of a functional, nonirradiated vagina.

Simple Hysterectomy (Type I)

Hysterectomy techniques vary depending on the degree of surrounding support that is resected and are categorized as type I, II, or III. Type I hysterectomy, also known as an *extrafascial hysterectomy* or *simple hysterectomy* , removes the uterus and cervix, but does require excision of the parametrium or paracolpium. It is appropriately selected for benign gynecologic pathology, preinvasive cervical disease, and stage IA1 cervical cancer.

Modified Radical Hysterectomy (Type II)

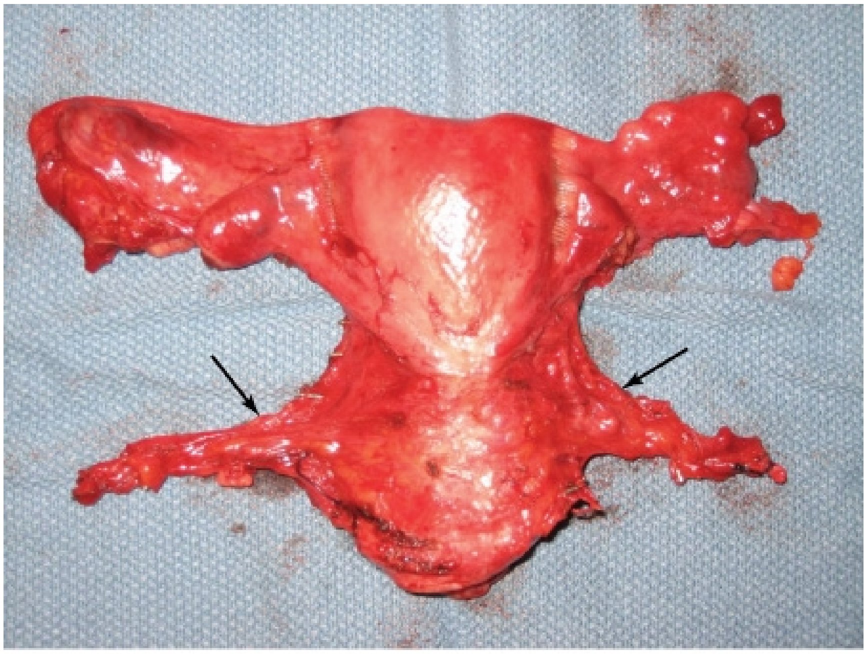
Modified radical hysterectomy removes the cervix, proximal vagina, and parametrial and paracervical tissue (see Section 43-2, Modified Radical Abdominal Hysterectomy (Type II)). The ureters are unroofed from the paracervical tunnel until their point of entry into the bladder. They are then retracted laterally to enable removal of the parametrial and paracervical tissue medial to the ureter. This hysterectomy is well suited for tumors with 3- to 5-mm depths of invasion and smaller stage IB tumors (Landoni, 2001).

Radical Hysterectomy (Type III)

This hysterectomy requires greater resection of the parametria, and excision extends to the pelvic sidewall (Fig. 30-13) (see Section 43-1, Radical Abdominal Hysterectomy (Type III)). The ureters are completely dissected from their beds, and the bladder and rectum are mobilized to permit this more extensive removal of tissue. In addition, at least 2 to 3 cm of proximal vagina is

resected. This procedure is performed for larger IB lesions, and for patients with relative contraindications to radiation such as diabetes, pelvic inflammatory disease, hypertension, collagen disease, or adnexal masses.

FIGURE 30-13



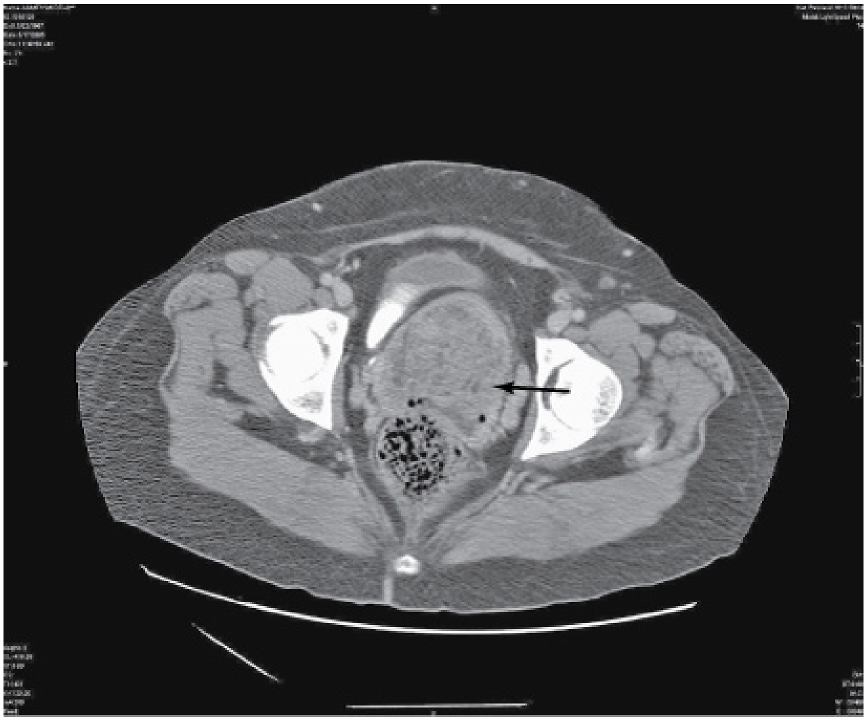
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Gross surgical specimen following radical hysterectomy. The specimen includes the uterus, adnexa, and parametria **(arrows)** .

STAGE IB TO IIA

Stage IB lesions are defined as those extending past the limits of microinvasion yet still confined to the cervix. This stage is subcategorized either as IB1 if tumors measure ≤4 cm or as IB2 if they measure >4 cm (Fig. 30-14).

FIGURE 30-14



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

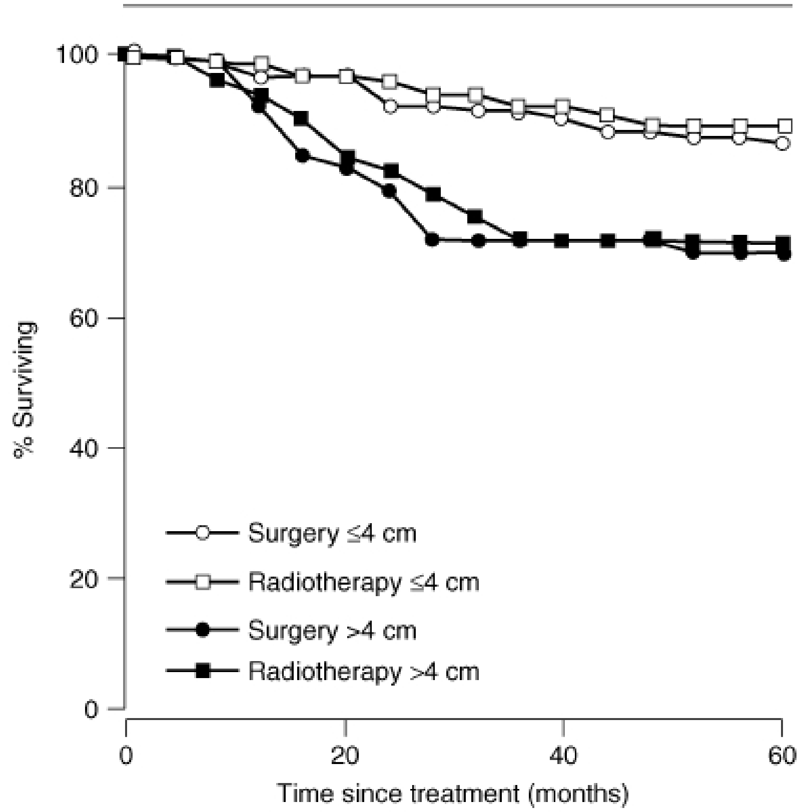
Computed tomography (CT) scan of stage IB2 cervical cancer. *(Courtesy of Dr. John Schorge.)*

Stage II cancers extend outside the cervix. They may invade the upper vagina and the parametria but do not reach the pelvic sidewalls. Stage IIA tumors have no parametrial involvement, but do extend vaginally as far as the proximal two thirds of the vagina. Stage IIB cancer may invade the vagina to a similar extent as well as invade the parametria.

Treatment of Stage IB to IIA Tumors

These cancers can be managed either with surgery or radiation therapy (Fig. 30-15). In a prospective study of primary therapy, 393 women were randomly assigned to undergo radical hysterectomy and pelvic lymphadenectomy or receive primary radiation therapy. Five-year overall survival and disease-free survival were statistically equivalent (83 percent and 74 percent, respectively). Surgical patients, however, had significantly greater severe morbidity rates compared with the radiotherapy group (Landoni, 1997).

FIGURE 30-15



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Graph shows equivalent overall survival rates whether stage IB through IIA tumors are treated surgically or with radiation therapy. *(From Landoni, 1997, with permission.)*

Because radiotherapy and surgery are both viable options, the optimum treatment for each woman ideally should assess clinical factors such as menopausal status, age, concurrent medical illness, tumor histology, and cervical diameter. For stage IB1 cervical cancers, it is left to the physician's discretion and patient preference as to which treatment modality is preferred. Our general approach to patients with stage IB2 and stage II cervical cancers is to manage them primarily with chemoradiation, in a similar fashion to advanced stage cervical cancers.

In general, radical hysterectomy for stage IB through IIA tumors is usually selected for young women with low BMIs who wish to preserve ovarian function and have concerns about altered sexual functioning following radiotherapy (see Chap. 28, Ovary and Pregnancy Outcomes). Age and weight are not contraindications to surgery, although in general, older women may have longer hospital stays and heavier women can have longer operative time, greater blood loss, and higher rates of wound complications. Surgery is contraindicated in patients with severe cardiac or pulmonary disease or prior thromboembolism.

In those electing surgery, oophorectomy may be deferred in younger women. One GOG study evaluated tumor spread to the ovary in those with IB tumors electing radical hysterectomy without adnexectomy. Ovarian metastases were identified in only 0.5 percent of 770 women with stage IB squamous cell cancers and in 2 percent of those with adenocarcinomas (Sutton, 1992).

Surgical and Radiotherapy Complications

Complications for early-stage cervical cancer surgery include ureteral stricture, bladder dysfunction, constipation, wound breakdown, lymphocyst, and lymphedema. In addition, radiotherapy added as an adjuvant to surgery increases the risk of these

complications.

On the other hand, radiation therapy also may be associated with long-term complications. Altered sexual function secondary to a shortened vagina, dyspareunia, psychological factors, and vaginal stenosis are often encountered. Late urinary and bowel complications such as fistula formation, enteritis, proctitis, and bowel obstruction may also develop following radiotherapy.

POSITIVE PELVIC LYMPH NODES

Approximately 15 percent of patients with stage I through IIA cervical cancers will have positive pelvic nodes. Risk factors for lymph node involvement include those listed in Table 30-8. Of those with involved nodes, 50 percent will have grossly positive pelvic nodes intraoperatively. In most cases, radical hysterectomy is abandoned, and whole-pelvic radiation with subsequent brachytherapy is administered.

Table 30-8 Frequency of Positive Pelvic Lymph Nodes by Pathologic Factors for Patients with Squamous Cell Carcinoma, No Gross Disease beyond the Uterus and Cervix, and Negative Aortic Nodes

Factor	**Frequency with Positive Pelvic Lymph Nodes (%)**		***p***
Histologic grade			
1	9/93	(9.7)	
2	52/373	(13.9)	0.01
3	39/179	(21.8)	
Keratinizing/cell type size classification			
Large cell nonkeratinizing	58/401	(14.5)	
Large cell keratinizing	39/227	(17.2)	0.6
Small cell/other	3/17	(17.6)	
Depth of invasion			
≤5 mm	6/177	(3.4)	
6â€“10 mm	36/238	(15.1)	
11â€“15 mm	30/135	(22.2)	0.0001
16â€“20 mm	19/49	(38.8)	
21+ mm	7/31	(22.6)	
Inner third	9/199	(4.5)	
Middle third	28/210	(13.3)	0.0001
Outer third	60/227	(26.4)	
Uterine extension			
Negative	83/567	(14.6)	

Positive	16/74	(21.6)	0.2
Surgical margins			
Negative	95/623	(15.2)	
Positive	5/20	(25.0)	0.4
Parametrial extension			
Negative	81/599	(13.5)	
Positive	19/44	(43.2)	0.0001
Capillary/lymphatic spaces			
Negative	30/366	(8.2)	
Positive	70/276	(25.4)	0.0001

From Delgado, 1990, with permission.

RECURRENCE RISK

Intermediate Risk of Recurrence

The GOG has defined recurrence risk factors that would identify women who undergo radical surgery for early-stage cervical cancer. *Intermediate risk* describes those who on average would have a 30-percent risk of cancer recurrence within 3 years. Factors included in this model are depth of tumor invasion, tumor diameter, and LVSI.

To determine appropriate treatment of these at-risk women, patients with these intermediate-risk factors have been studied. In one study, women were randomly assigned to receive pelvic radiation therapy following radical hysterectomy or radical hysterectomy and observation. A nearly 50-percent reduced risk of recurrence was found in those who received postoperative adjuvant radiation therapy (Sedlis, 1999). However, this adjuvant radiation does not prolong overall survival. In our practice, these intermediate-risk patients are counseled regarding their risk of recurrence and offered the option of adjuvant radiation therapy.

High Risk of Recurrence

A high-risk category of patients who undergo radical surgery for early-stage cervical cancer has also been described. *High-risk* is defined as a 50- to 70-percent risk of recurrence within 5 years. These women have positive lymph nodes, positive surgical margins, or microscopically positive parametria (Peters, 2000).

This group is routinely offered adjuvant radiation therapy. Moreover, the GOG recently demonstrated that the addition of concurrent chemotherapy consisting of cisplatin and 5-FU would be beneficial in significantly prolonging disease-free and overall survival in this group of women with high-risk early stage cancer (Peters, 2000).

Adjuvant Hysterectomy Following Primary Radiation

Benefits of treating bulky stage I (IB2) cervical cancers with adjuvant hysterectomy following radiation therapy has been evaluated. Adjuvant hysterectomy reduces locoregional relapse, but does not contribute to an overall improvement in survival. However, initial lesion size may affect efficacy. In one study, those with tumors measuring less than 7 cm who underwent postradiation hysterectomy survived longer compared with women with equivalent tumors in the radiation-only regimen group. In contrast, those with lesions 7 cm or larger who underwent postradiation hysterectomy fared worse than their counterparts receiving only radiotherapy (Keys, 2003).

EARLY STAGE CERVICAL ADENOCARCINOMA

These cancers may be more radioresistant than squamous cell cervical carcinomas. Although some prefer radical hysterectomy to radiotherapy, studies suggest equivalent survival rates with both (Eifel, 1990, 1991, 1995; Hopkins, 1988; Nakano, 1995). However, larger lesions may not regress if managed by radiation alone (Leveque, 1998; Silver, 1998). In bulky tumors, their centers may be less radiosensitive due to relative cellular hypoxia (see Chap. 28, Radiation Biology). This effect underscores the advantages of radical hysterectomy for women with stage I cervical adenocarcinoma.

STAGES IIB THROUGH IVA

Advanced-stage cervical cancers extend past the confines of the cervix and often involve adjacent organs and retroperitoneal lymph nodes. As such, treatment for these tumors must be individualized to maximize patient outcome. The vast majority of advanced-stage tumors have poor prognosis, and 5-year survival rates are less than 50 percent. Advanced-stage tumors represent a large proportion of invasive cervical cancers treated, depending on the geographic area studied. If untreated, these tumors progress rapidly.

Radiation Therapy

This modality forms the cornerstone of advanced-stage cervical cancer management. Both external beam pelvic radiation and brachytherapy are typically delivered (see Chap. 28, Radiation Therapy). Of these, external beam radiation usually precedes intracavitary radiation, which is one form of brachytherapy. External beam radiation is commonly administered in 25 fractions during 5 weeks. During brachytherapy, to limit bladder and rectal doses, bowel and bladder are packed away from the intracavitary source during tandem insertion, using vaginal packing. During staging, if para-aortic nodal metastases are found, then extended field radiation can be added to treat these affected lymph nodes.

Chemoradiation

Current evidence indicates that concurrent chemotherapy significantly improves overall and disease-free survival of women with advanced cervical cancer. Thus, most patients with stage IIB through IVA cervical cancer are best treated with chemoradiation. Cisplatin-containing regimens have been associated with the best survival rates (Rose, 1999b; Whitney, 1999). Chemoradiation is also associated with superior survival rates compared with pelvic and extended field para-aortic region irradiation alone (Morris, 1999). At our institution, cisplatin is given weekly for 5 weeks and is administered concurrently with radiotherapy.

Pelvic Exenteration for Primary Disease

This surgery encompasses removal of the bladder, rectum, uterus (if present), and surrounding tissues (see Section 43-3, Total Pelvic Exenteration). Primary exenteration may be considered for women with stage IVA cancer, that is, with direct tumor invasion into bladder and/or bowel without distant spread. For this indication, however, it is rarely performed. Yet for women with stage IVA cervical cancer and extension solely into the bladder, the survival rate can reach 30 percent (Million, 1972; Upadhyay, 1988).

STAGE IVB

Patients with stage IVB disease have a poor prognosis and are treated with a goal of palliation. Pelvic radiation is administered to control vaginal bleeding and pain. Systemic chemotherapy is offered to palliate symptoms. The chemotherapy regimens used in this group of women is similar to those used in the setting of recurrent cancer.

Surveillance

FOLLOWING RADIOTHERAPY

Women who receive radiotherapy should be closely monitored to assess their response. Tumors may be expected to regress for up to 3 months after therapy. Pelvic examination and/or radiologic scanning should document progressive shrinkage of the cervical mass. The rectovaginal examination should be used to detect nodularity in the ligaments and parametria. If disease progresses locally after this interval, surgery should be considered. Typically, pelvic exenteration is indicated for this clinical setting.

In addition to pelvic examination, a thorough manual nodal survey should include neck, supraclavicular, infraclavicular, axillary, and inguinal lymph nodes. In addition, a chest radiograph can be obtained yearly. Cervical or vaginal cuff Pap smear should also be collected every 3 months for 2 years and then every 6 months for 3 years. Findings of low-grade or high-grade squamous intraepithelial lesion should prompt colposcopic evaluation. If high-grade lesion or cancer is noted on cervical biopsy, then CT

scanning to assess disease recurrence is indicated.

FOLLOWING SURGERY

After a radical hysterectomy, 80 percent of recurrences are detected within the subsequent 2 years. During patient surveillance, identification of an abnormal pelvic mass or abnormal pelvic examination, pain radiating down the posterior thigh, or new-onset lower extremity edema should prompt CT scanning of the abdomen and pelvis. Pelvic recurrences after radical hysterectomy, if diagnosed early, can be salvaged with radiation therapy.

Secondary Disease

Secondary disease is defined as either persistent or recurrent cancer. Cervical cancer that has not completely regressed within 3 months of radiotherapy is considered persistent. Disease recurrence is defined as a new lesion after completion of primary therapy.

Treatment of persistent or recurrent disease depends on its location and extent. The intent in these cases is usually palliative. However, in certain instances, a woman may qualify for pelvic radiation if she previously had not received this treatment. Alternatively, a woman may be a candidate for a curative-intent surgical procedure. All chemotherapy-based treatments of metastatic disease are administered with a goal of palliation. In these cases, the primary focus is to maximize existing patient quality of life.

PELVIC EXENTERATION FOR SECONDARY DISEASE

When curative-intent surgery is contemplated, local disease should be biopsy proven. Clinically, a patient may be considered for pelvic exenteration if lower extremity edema, back pain, and hydronephrosis are absent. If present, these suggest disease extension to the pelvic side walls, which would contraindicate surgery. In addition, regional and distant metastasis should be excluded by both physical examination and radiologic imaging.

Pelvic exenteration begins with exploratory laparotomy, biopsies of suspicious lesions, and pelvic and para-aortic lymph node evaluation. Exenteration is completed only if there is no disease in frozen section specimens sampled during surgery. A complete surgical description of this procedure is found in Section 43-3, Total Pelvic Exenteration.

Alternatively, in highly selected patients radical hysterectomy may be considered an alternative to pelvic exenteration (Coleman, 1994). In these circumstances, women should have small cervical recurrences measuring less than 2 cm and have disease-free pelvic lymph nodes both prior to and during surgery. With either surgical procedure, intraoperative and postoperative complications can be significant.

RADIOTHERAPY FOR SECONDARY DISEASE

Patients with central or limited peripheral recurrences who are radiotherapy naive are candidates for curative-intent radiation treatment. In these groups, survival rates of 30 to 70 percent have been reported (Ijaz, 1998; Ito, 1997; Lanciano, 1996; Potter, 1990).

CHEMOTHERAPY FOR SECONDARY DISEASE

Antineoplastic drugs are used to palliate both disease and symptoms of advanced, persistent, or recurrent cervical cancer (Table 30-9). Cisplatin is considered the single most active cytotoxic agent in this setting (Thigpen, 1995). Overall, response duration to cisplatin is 4 to 6 months, and survival in such women only approximates 7 months (Vermorken, 1993). Recently, a prospective randomized study demonstrated that the combination of cisplatin with topotecan confers a survival advantage to this group of patients, compared with cisplatin alone (GOG protocol #179). Moreover, ongoing GOG studies aim to determine the best combination cytotoxic chemotherapy for women with recurrent or persistent cervical cancer.

Table 30-9 Combination Chemotherapy Regimens and Response Rates of Cervical Cancer				
Study	**Chemotherapy Agents**	**Response Rates**	**Progression-free Survival**	**Overall Survival**
Moore, 2004	Cisplatin vs. cisplatin and taxol (Phase III)	19% vs. 36%	2.8 vs. 4.8 months	No difference
Long, 2005	Cisplatin vs. cisplatin and topotecan (Phase III)	13% vs. 27%	2.9 vs. 4.6 months	6.5 vs. 9.4 months
Morris, 2004	Cisplatin and vinorelbine (Phase II)	30%	5.5 months	
Brewer, 2006	Cisplatin and gemcitabine (Phase II)	22%	2.1 months	

Palliative Care

Palliative chemotherapy is administered only if this treatment does not cause significant decline in patient quality of life. Any decision for treatment of cervical cancer in a palliative care setting should be assessed against the benefits of supportive care. Women with persistent nausea and vomiting from tumor-associated ileus may benefit from a gastrostomy tube. Urinary fistulas and bowel obstruction can be managed surgically, provided a patient is an appropriate surgical candidate. Pain management forms the basis of palliation and an extensive list of pain medications is found in Table 39-15.

We recommend discussion of medical directives if a patient has adequate mental capability. Often, such discussion is conducted over time, giving a woman an opportunity to understand the nature and progression of her disease. Home hospice is an invaluable part of terminal care for most of these women, who require intense pain management and considerable assistance with daily living activities.

Management during Pregnancy

There is no difference in survival between pregnant and nonpregnant women with cervical cancer when matched by age, stage, and year of diagnosis. As with nonpregnant women, clinical stage at diagnosis is the single most important prognostic factor for cervical cancer during pregnancy. Overall survival is slightly better for cervical cancer in pregnancy because an increased proportion of patients have stage I disease.

DIAGNOSIS

A Pap smear is recommended for all pregnant patients at the initial prenatal visit. Additionally, clinically suspicious lesions should be directly biopsied. If Pap test results reveal HSIL or suspected malignancy, then colposcopy is performed and biopsies are obtained. However, endocervical curettage is excluded. If Pap testing indicates malignant cells and colposcopic-directed biopsy fails to confirm malignancy, then diagnostic conization may be necessary. Conization is recommended only during the second trimester and only in patients with inadequate colposcopic findings and strong cytologic evidence of invasive cancer. Conization is deferred in the first trimester, as this surgery is associated with abortion rates of 30 percent in this part of pregnancy.

STAGE I CANCER IN PREGNANCY

Women with microinvasive squamous cell cervical carcinoma measuring 3 mm or less and containing no LVSI may deliver vaginally and be re-evaluated 6 weeks postpartum. Moreover, for those with stage IA or IB disease, studies find no increased maternal risk if treatment is intentionally delayed to optimize fetal maturity regardless of the trimester in which the cancer was diagnosed. Given the outcomes, a planned treatment delay is generally acceptable for women who are 20 or more weeks' gestational age at diagnosis with stage I disease and who desire to continue their pregnancy. However, a patient may be able to delay from earlier gestational ages if she wishes.

ADVANCED CERVICAL CANCER IN PREGNANCY

Women with advanced cervical cancer diagnosed prior to fetal viability are offered primary chemoradiation. Spontaneous abortion

of the fetus tends to follow whole-pelvis radiation therapy. If cancer is diagnosed after fetal viability is reached and a delay until fetal pulmonary maturity is elected, then a classical cesarean delivery is performed. A classical cesarean incision minimizes the risk of cutting through tumor in the lower uterine segment, which can cause serious blood loss. Chemoradiation is administered after uterine involution. For patients with advanced disease and treatment delay, pregnancy may impair prognosis. Women who elect to delay treatment, to provide quantifiable benefit to their fetus, will have to accept an undefined risk of disease progression.

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INVASIVE CANCER OF THE VULVA: INTRODUCTION

Vulvar cancer is primarily a disease of elderly women but has been observed in premenopausal women as well. These cancers are uncommon and comprise approximately 5 percent of all gynecologic malignancies. As a result, a general clinician's experience with these lesions may be limited.

Vulvar tumors typically produce symptoms of pruritus and irritation. Minor symptoms may be initially ignored by women, contributing to a delay in diagnosis. Additionally, diagnostic delays may follow topical therapy by providers for presumed other dermatoses prior to establishing a pathologic diagnosis. Thus, early detection and biopsy of any abnormal vulvar lesion are imperative to diagnosing vulvar cancer in its early stages.

Almost 90 percent of vulvar tumors are squamous cell carcinomas. Accordingly, virtually all knowledge regarding prognostic factors, spread patterns, and survival information is based on review of women with this tumor type. Although rare, uncommon histologic subtypes such as melanomas, basal cell carcinomas, Bartholin gland adenocarcinomas, and various other soft tissue sarcomas also may be encountered (Table 31-1).

Table 31-1 Incidence of Vulvar Neoplasms by Histologic Type[a]

Tumor Type	Percent	
Epidermoid	86.2	
Melanoma	4.8	
Sarcoma	2.2	
Basal cell	1.4	
Bartholin gland		
Squamous	0.4	1.2
Adenocarcinoma	0.6	
Adenocarcinoma	0.6	
Undifferentiated	3.9	

[a] Based on 1,378 reported cases.

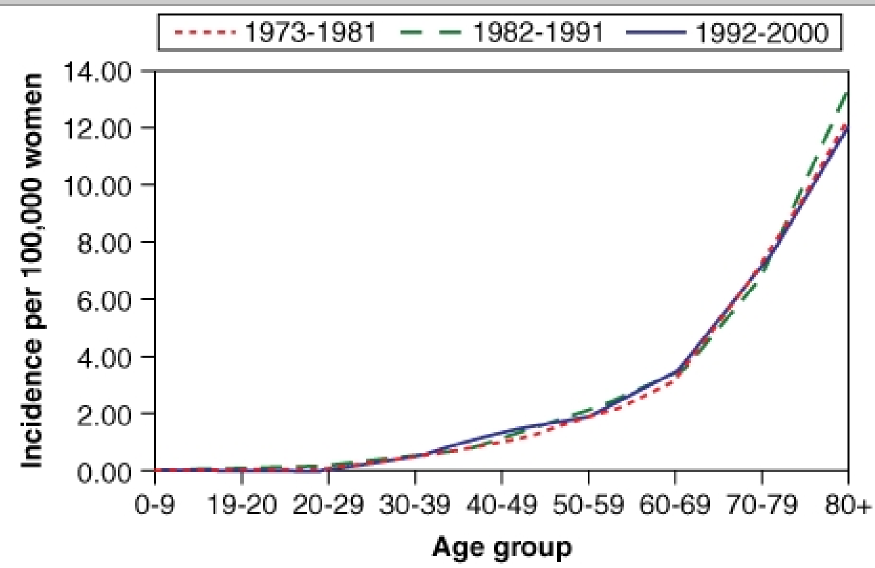
Modified from Plentl, 1971, with permission.

Most vulvar squamous cell cancers, when found early, carry a good prognosis. Traditional therapy includes radical excision of the vulva and inguinal lymph nodes. Adjuvant radiation therapy is instituted occasionally. Despite its infrequency, vulvar cancer remains an important female disease because of its significant impact on sexuality. Over the past decade, numerous advances have been made in the management of vulvar cancer, with a trend toward more conservative surgery and improved psychosexual outcomes.

INCIDENCE

Vulvar cancer's incidence increases steadily with age and peaks in the seventh decade of life (Cavanagh, 1986; Green, 2000; Morgan, 1999; Taussig, 1949; Thomas, 1991; Trope, 1991; Way, 1960) (Fig. 31-1). For this reason, the steady increase in life expectancy has brought carcinoma of the vulva increased attention among gynecologic malignancies.

FIGURE 31-1



The incidence of invasive vulvar cancer increase with age. *(From Judson, 2002, with permission.)*

According to the National Center for Health Statistics and the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute 2006 data, there were an estimated 3,740 new cases of vulvar cancer and 880 deaths (Jemal, 2006). Vulvar cancer has an age-adjusted death rate of 0.2 per 100,000 women according to the 2000 U.S. standard population.

PATHOPHYSIOLOGY

Most vulvar malignancies arise within squamous epithelium. Although the vulva does not have an identifiable transformation zone, squamous neoplasias arise most commonly at the border of vulvar keratinized stratified squamous epithelium and the nonkeratinized squamous mucosa of the vestibule. In addition, most vulvar cancers arise within recognized areas of epithelial cell abnormality. For example, approximately 60 percent of cases have adjacent vulvar intraepithelial neoplasia (VIN), and 15 to 40 percent of cases are associated with lichen sclerosus.

Human Papillomavirus Infection

Based on etiologic and histopathologic characteristics, vulvar squamous cell carcinoma is suspected to develop via two separate pathways. One pathway leads mainly to nonkeratinizing (basaloid and/or warty) carcinomas and primarily affects younger women. In this pathway, infection with high-risk human papillomavirus (HR-HPV) is found. Serotypes 16 and 18 predominate, although HPV serotypes 18, 31, 33, and 45 also have been reported (see Chap. 29, Incidence) (van der Avoort, 2006). This type of carcinoma in general carries a significantly better prognosis than HPV-negative cancer.

The second pathway is rarely associated with HR-HPV, occurs in older women, leads to mostly differentiated keratinizing squamous cell carcinoma, and develops in a background of nonneoplastic epithelial disorders, such as lichen sclerosus.

Patterns of Spread

Vulvar cancers spread via the classic mechanisms of malignancy, which include local growth and extension into adjacent organs, embolization into regional lymph nodes, and hematogenous dissemination to distant sites.

HEMATOGENOUS SPREAD

Blood supply to the vulva is derived primarily from the internal pudendal vessels, which stem from an anterior branch of the internal iliac vessels (see Fig. 38-22). The internal pudendal vessels exit the pelvis and travel around the ischial spine to reach the posterolateral vulva and divide into several smaller branches to supply the vulva (see Fig. 38-28).

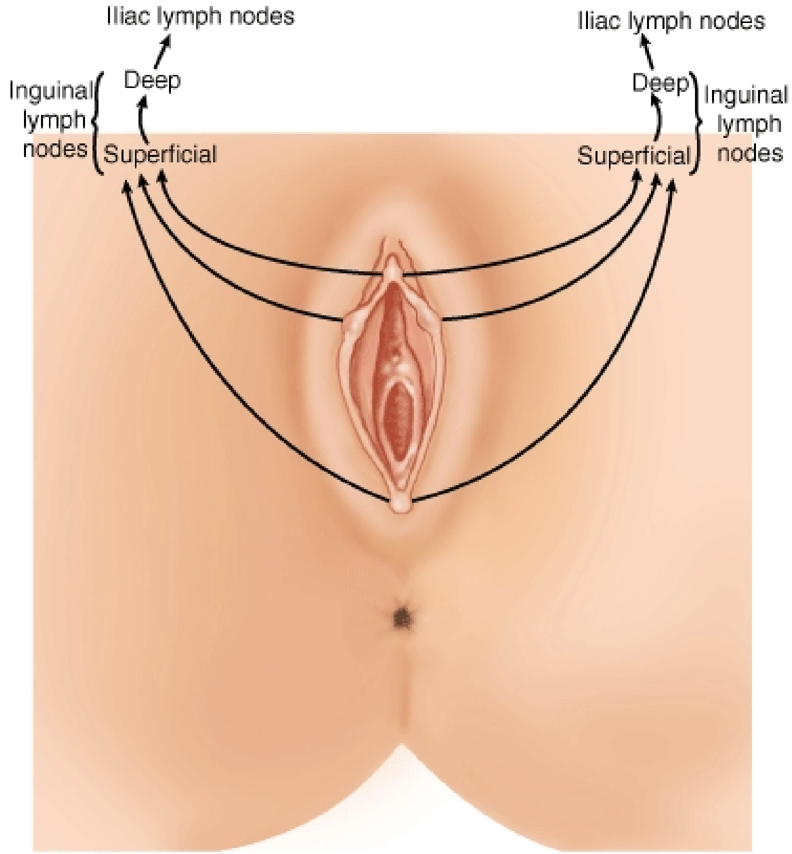
The deep external pudendal artery and the superficial pudendal artery are branches of the femoral artery that drain into the great saphenous vein (see Fig. 38-29). Both arteries supply the labia majora and their deep structures. They share anastomotic connections with branches of the internal pudendal vessels in areas where their tributaries mutually contribute blood supply.

LYMPHATIC SPREAD

Lymphatic vessels of the vulva drain primarily into the superficial inguinal lymph nodes. These nodes are located within a triangle formed by the inguinal ligament, the medial border of the sartorius muscle, and the lateral border of the adductor longus muscle (see Fig. 38-29). The phrase *pelvic lymph nodes* collectively defines the iliac and obturator lymph nodes, whereas the term *inguinofemoral lymph nodes* is often used to describe the collective deep and superficial inguinal nodes.

In general, lymphatic drainage travels in a stepwise fashion from the superficial to the deep inguinal nodes and then to pelvic lymph nodes (Fig. 31-2). Any spread beyond the inguinal nodes is considered distant metastasis.

FIGURE 31-2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Typical lymphatic drainage pattern with vulvar cancer. *(From Stenchever, 2001, with permission.)*

Vulvar lymphatics decussate in the mons pubis and the posterior fourchette. Lymphatics do not cross the labiocrural folds and generally do not cross the midline unless originating at the clitoris or at the perineal body (Morley, 1976). As a result, metastasis to contralateral nodes is rare in the absence of ipsilateral groin metastasis. *Ipsilateral* tumors can be defined as lesions that are further than 1 cm from the midline.

Infrequently, aberrant channels course directly from the tumor to ipsilateral deep inguinal or pelvic lymph nodes or to contralateral lymph nodes. These anatomic variants ultimately may explain unanticipated cancer recurrence following lymph node dissection in which no nodal metastasis was found.

With vulvar cancer, in-transit metastases are rare and suggest that initial lymphatic spread within the vulvar skin is exceedingly uncommon. In general, *in-transit metastases* are those that develop within regional dermal and subdermal lymphatics before reaching superficial inguinal nodes. These metastases lie more than 2 cm from the primary lesion but within the inguinal nodal drainage basin. In-transit metastases are differentiated from *satellite lesions,* which are skin or subcutaneous lesions within 2 cm of the primary tumor. These are considered intralymphatic extensions of the primary mass.

EPIDEMIOLOGY AND RISK FACTORS

As described earlier, two models for development of vulva cancer have been suggested, and risk factors for these two types vary (Table 31-2).

Table 31-2 Models of Vulvar Cancer

Characteristic	Type 1	Type 2
Age	Younger (35â€“65 years)	Older (55â€“85 years)
Cervical neoplasia	High association	Low association
Cofactors	Age, immune status, viral integration	Vulvar atypia, possibly mutated host genes
Histopathology of tumor	Intraepithelial-like (basaloid), poorly differentiated	Keratinizing; squamous cell carcinoma, well differentiated
HPV DNA	Frequent (>60%)	Seldom (<15%)
Pre-existing lesion	VIN	Vulvar inflammation, lichen sclerosus, squamous cell hyperplasia
History of condyloma	Strong association	Rare association
History of STD	Strong association	Rare association
Cigarette smoking	High incidence	Low incidence

HPV = human papillomavirus; VIN = vulvar intraepithelial neoplasia; STD = sexually transmitted disease.

Adapted from Crum, 1992, with permission.

Infection

HERPES SIMPLEX VIRUS

This infection has been shown to have a strong association with vulvar cancer in several studies. However, the association is more prominent when combined with other cofactors such as smoking (Madeleine, 1997). Thus, the presence of herpes simplex virus (HSV) alone in association with vulvar cancer as a causative factor for should not be considered conclusive.

HUMAN PAPILLOMAVIRUS

More recently, human papillomavirus (HPV) infection has been associated with vulvar cancer. For example, women positive for HPV serotype 16 show a higher risk of developing vulvar cancer. Moreover, HPV DNA from oncogenic HPV serotypes 16 and 18 has been isolated from carcinomatous and in situ lesions of the vulva (Ansink, 1994; Downey, 1988). However, there are stronger correlations between in situ vulvar lesions and HPV than with frankly invasive lesions and viral infection (Hildesheim, 1997). In addition, HPV DNA can be identified in 70 to 80 percent of intraepithelial lesions but is seen in only 10 to 50 percent of invasive lesions. These latter points support the idea that vulvar cancer develops along two distinct pathways, either with or without HPV.

Similar to HSV, the presence of HPV becomes a stronger risk for vulvar cancer when combined with other cofactors such as smoking and HSV infection (Madeleine, 1997). Women who have smoked and have a history of genital warts have a 35-fold increased risk for developing vulvar cancer compared with women without these factors (Brinton, 1990; Kirschner, 1995).

Immunosuppression

Chronic immunosuppression has been indirectly associated with vulvar cancer and is thought to contribute to persistent HPV and HSV infections. Specifically, vulvar cancer rates have been shown to be increased in women with HIV infection (Elit, 2005; Frisch,

2000).

Lichen Sclerosus

This chronic vulvar inflammatory disease has been particularly linked to the development of vulvar cancer and is discussed further in Chapter 4, Lichen Sclerosus. Although not validated as a causative or precursor lesion, current evidence suggests a correlative relationship between the two. Keratinocytes affected by lichen sclerosus show a proliferative phenotype and can exhibit markers of neoplastic progression. This suggests that lichen sclerosus may be a precursor lesion to invasive squamous vulvar cancer (Rolfe, 2001). Vulvar cancers that coexist with lichen sclerosus have been shown to develop in older women, predominate at or near the clitoris, and lack association with vulvar intraepithelial neoplasia (VIN).

Vulvar Intraepithelial Neoplasia

The natural history of VIN type 3 is unclear. On the one hand, the progression of VIN 3 to invasive cancer has been strongly suggested. Although most of VIN 3 lesions do not progress, several reports have demonstrated that in a small percentage of women older than 30 years, untreated lesions can progress to invasive cancer within a mean of 4 years (Jones, 2005; van Seters, 2005).

However, some cases of progression may reflect misdiagnosis. For example, a recent meta-analysis evaluated data from 3,322 women who were treated for VIN 3. Investigators found that occult carcinomas were diagnosed in the final pathology specimen in 3.2 percent of patients, and 3.3 percent of carcinomas were diagnosed during postoperative surveillance (van Seters, 2005). In addition, although recent reports have shown that the rate of VIN 3 has increased by 411 percent within the past 30 years, the rate of invasive squamous carcinoma of the vulva has risen a modest 20 percent (Judson, 2006). These observations suggest that aggressive treatment of preinvasive disease has not prevented the development of invasive tumors. Thus, the causes of in situ and invasive lesions may not be strongly related, or affected women may not have not yet reached the age at which invasive lesions are seen. An additional discussion of VIN is found in Chapter 29, Incidence.

SYMPTOMS

Most women with VIN and vulvar cancer present with pruritus and a visible lesion, although pain, bleeding, and ulceration also may be initial complaints (see Table 29-14). Most patients experience symptoms for weeks or months before diagnosis. Patient embarrassment and clinical unfamiliarity, as well as provider reluctance to fully evaluate symptoms, often adds to the delay.

A well-defined mass is not always present , especially in younger women with multifocal disease. Moreover, selecting the appropriate site for tissue sampling may be challenging. In such cases, multiple biopsies may be required during colposcopic examination of the vulva, termed *vulvoscopy* . Other clinical entities may present similarly and include preinvasive neoplasia, infection, chronic inflammatory disease, and granulomatous disease. Thus, the goal of evaluation should be to obtain an accurate and definitive pathologic diagnosis.

DIAGNOSIS

Lesion Evaluation

At the initiation of vulvoscopy, the vulva is soaked with 3% acetic acid for 5 minutes. This allows for adequate penetration into the keratin layer and aids identification of acetowhite areas and abnormal vascular patterns (see Chap. 29, Colposcopy). The entire vulva and perianal skin should be examined systematically. Lesions may be raised, ulcerated, pigmented, or warty, and biopsies of the most suspicious-appearing areas are obtained as described in Chapter 4, Vulvar Biopsy. Specimens removed with a Keyes punch forceps should be approximately 4 mm thick to include the surface epithelial lesion and the underlying stroma. This allows evaluation for the presence and depth of lesion invasion. Colposcopic examination of the cervix and vagina and careful examination of the perianal area are recommended to diagnose any synchronous or associated neoplasm of the lower genital tract. Women who have a well-defined mass should have a direct biopsy sent for pathologic evaluation.

Cancer Patient Evaluation

A complete evaluation of the woman with vulvar cancer requires assessment of the clinical extent of disease and coexisting medical

illnesses. Thus, detailed physical examination includes measurement of the primary tumor and evaluation of extension into other areas of the genitourinary system, the anal canal, the bony pelvis, and inguinal lymph nodes. At our institution, if a thorough physical is not possible secondary to patient discomfort or extent of disease, an examination under anesthesia is performed together with cystourethroscopy or proctosigmoidoscopy or both if suspicion of tumor invasion into the urethra, bladder, or anal canal is high.

Women with small tumors and clinically negative groin lymph nodes require few additional diagnostic studies other than those needed for surgical preparation. Additional radiologic studies such as computed tomographic (CT) scanning, magnetic resonance (MR) imaging, and intravenous pyelography are recommended in women with larger tumors to exclude local invasion, lymph node involvement, and metastatic disease. For some patients with advanced tumors, fine-needle aspiration biopsy from sites of suspected metastases may eliminate the need for surgical exploration.

Staging Systems

Currently, the International Federation of Gynecology and Obstetrics (FIGO) advocates surgically staging of a woman with vulvar cancer. In 1988, FIGO adopted a staging system that is based on a tumor, nodal, metastatic (TNM) classification. Thus, staging involves primary tumor resection to obtain tumor dimensions and dissection of superficial and deep inguinal lymph nodes for evaluation of tumor spread. In women with larger tumors or with metastatic inguinal lymph nodes, chest radiograph and either CT scanning or MR imaging of the abdomen and pelvis are also obtained preoperatively to determine the presence or absence of metastatic disease.

In 1995, FIGO instituted a subclassification of stage I tumors. In this group, stage IA lesions were 2 cm or smaller, were confined to the vulva or perineum, and displayed stromal invasion no greater than 1 mm. These lesions, termed *microinvasive cancers,* reflect a subpopulation in which the risk of inguinal metastasis is negligible (Binder, 1990; Donaldson, 1981; Hacker, 1984). The remainder of stage I lesions, classified as stage IB, are lesions of equivalent external dimensions but with stromal invasion greater than 1 mm (Table 31-3).

Table 31-3 FIGO Staging of Invasive Cancer of the Vulva

Stage 0	
Tis	Carcinoma in situ, intraepithelial carcinoma
Stage I	
T1 N0 M0	Tumor confined to the vulva and/or perineum, 2 cm or less in greatest dimension (no nodal metastasis)
	Stage IA Lesions 2 cm or less in size confined to the vulva or perineum and with stromal invasion no greater than 1.0 mm[a] (no nodal metastasis)
	Stage IB Lesions 2 cm or less in size confined to the vulva or perineum and with stromal invasion greater than 1.0 mm (no nodal metastasis)
Stage II	
T2 N0 M0	Tumor confined to the vulva and/or perineum, more than 2 cm in greatest dimension (no nodal metastasis)
Stage III	
T3 N0 M0	Tumor any size with
T1 N1 M0	(1) Adjacent spread to the lower urethra and/or the vagina or the anus, and/or
T2 N1 M0	(2) Unilateral regional lymph node metastasis

Stage IVA	
T1 N2 M0	Tumor invades any of the following: upper urethra, bladder, mucosa, rectal mucosa, pelvic bone, and/or bilateral regional node metastasis
T2 N2 M0	
T3 N2 M0	
T4 Any N M0	
Stage IVB	
Any T Any N M1	Any distant metastasis including pelvic lymph nodes

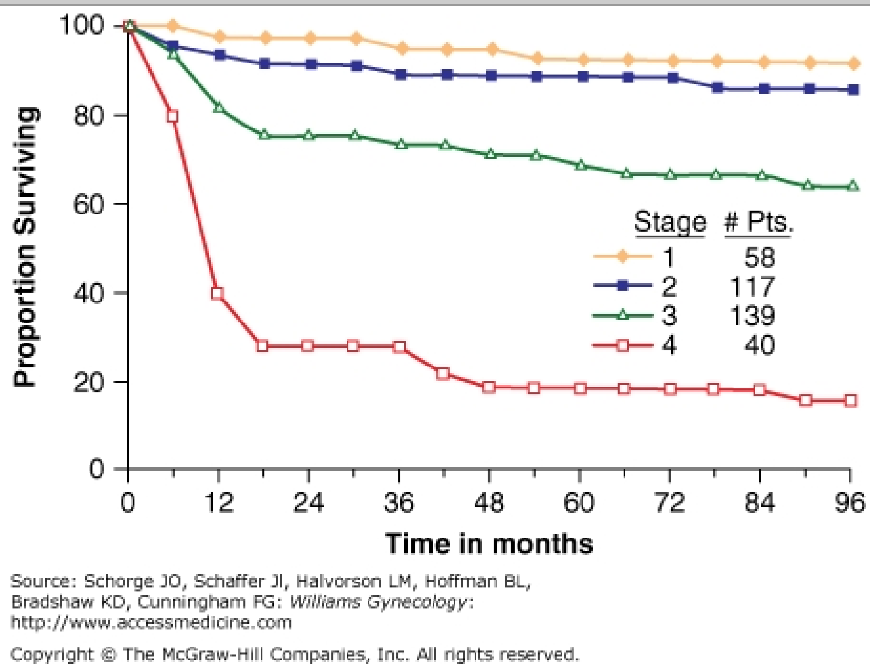
[a] The depth of invasion is defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.

From DiSai, 1997, with permission.

PROGNOSIS AND PROGNOSTIC FACTORS

The overall survival rates of women with squamous cell carcinoma of the vulva are excellent. Five-year survival rates of 80 to 90 percent are reported routinely for stage I and II disease. As anticipated, survival rates for higher stages are poorer. Rates of 48 percent for stage III and 15 percent for stage IV have been noted (Fig. 31-3). Numerous studies indicate that tumor stage, especially lymph node involvement; tumor thickness; location on the vulva; lymphatic vascular space involvement (LVSI); and histologic differentiation are all important prognostic factors for women with vulvar cancer.

FIGURE 31-3



Survival curves of women with invasive vulvar cancer grouped by FIGO stage. *(From Hoskins, 2000, with permission.)*

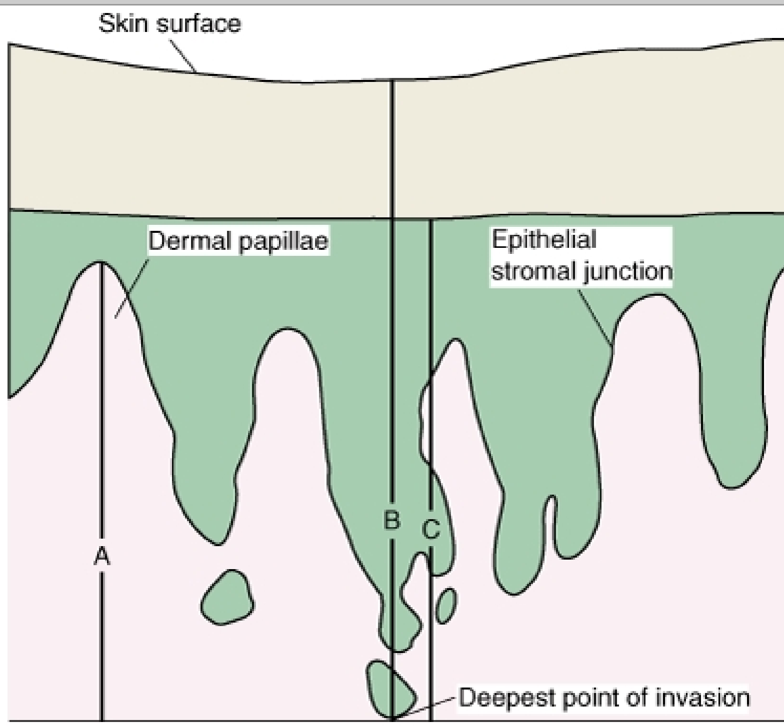
Lymph Node Metastasis

Lymph node metastasis is the single most important prognostic factor in vulvar cancer. The presence of inguinal node metastasis reduces long-term survival by 50 percent (Farias-Eisner, 1994; Figge, 1985). Among patients who have inguinal lymph node metastasis, factors that further delineate a poorer prognosis include bilateral involvement, extracapsular invasion, and increased dimension of lymph node metastasis if only one node is involved.

Nodal status is determined by surgical resection and pathologic evaluation. Independent predictors that increase the risk for nodal metastasis include less tumor differentiation; suspicious, fixed, or ulcerated nodes; and presence of lymphatic vascular space involvement (LVSI), older age, and increasing tumor thickness. Lesion size and location, however, are not associated factors (Homesley, 1993).

Tumor thickness is measured from the overlying surface epithelium to the deepest point of invasion, as specified by the International Society of Gynecological Pathologists, the World Health Organization, and FIGO (Creasman, 1995; Kalnicki, 1987; Scully, 1994) (Fig. 31-4). However, if a lesion is keratinized, then lesion thickness is measured from the granular layer to the greatest depth of tumor invasion. Tumors with a thickness of less than 1 mm carry little or no risk of groin metastasis, and increasing rates of metastasis are associated increasing thickness.

FIGURE 31-4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Histologic measurement of invasive vulvar cancers. **A.** Depth of invasion is measured from the junction between the epithelium and stroma of the most superficial dermal papilla to the greatest depth of tumor invasion. **B.** If a lesion is nonkeratinized, lesion thickness is measured from the lesion surface to the greatest depth of tumor invasion. **C.** If a lesion is keratinized, lesion thickness is measured from the granular layer to the greatest depth of tumor invasion. *(From Hoskins, 2000, with permission.)*

Surgical Margins

The risk of local recurrence is also related to surgical margin adequacy. A study by Heaps and co-workers (1990) showed that a 1-cm tumor-free surgical margin results in a high rate of local control, whereas margins less than 8 mm are associated with a 50-percent chance of recurrence. Although obtaining adequate margins may reduce the rate of vulvar cancer recurrence significantly, there is no evidence that simply taking wider margins will prevent local recurrences. Most recurrences owing to "residual" tumor

occur within a period of 2 years of primary therapy. Local recurrences seen after 2 years are more likely to be new tumors. Prevention of these late recurrences is less likely to be influenced by extending margins beyond 1 cm.

Lymphatic Vascular Space Invasion

Lymphatic vascular space invasion (LVSI) and association of a tumor with VIN 2 or 3 also predict early disease recurrence (Preti, 2005). For example, squamous cell carcinoma of the vulva with LVSI is associated with a higher frequency of lymph node metastasis and a lower overall 5-year survival rate (Hoskins, 2000).

Tumor Growth Pattern

Invasive vulvar cancer has two predominant growth patterns: moderately to poorly differentiated squamous cell carcinoma and keratinizing squamous carcinoma. Moderately to poorly differentiated carcinoma is frequently associated with HPV nuclei and sheets of immature neoplastic cells with a high nuclear:cytoplasmic ratio. There is a tendency for cohesive growth and a loss of cell polarity with a tendency to form irregular interconnecting sheets of tumor cells. These tumors are often (but not invariably) associated with HPV and VIN.

In contrast, keratinizing squamous carcinomas exhibit conspicuous maturation and keratinization. The basal cells appear to show mild to moderate atypia, with reduced atypia in the mature cells. These tumors fall into two general subcategories. The first consists of tumors organized into cohesive-appearing nests with a tendency toward blunt invasion intermixed with focal frank invasion. The second consists of tumors that are less well organized and invade the stroma with branching tongues and separate small cohesive units of well-differentiated tumor cells. These tumors are frequently associated with differentiated VIN and inflammatory dermatoses and often are HPV-negative (Crum, 2006).

Other patterns of growth invasion that are seen occasionally include verrucous carcinoma, papillary squamous carcinoma, and spindle cell squamous carcinoma. These patterns of growth are rare.

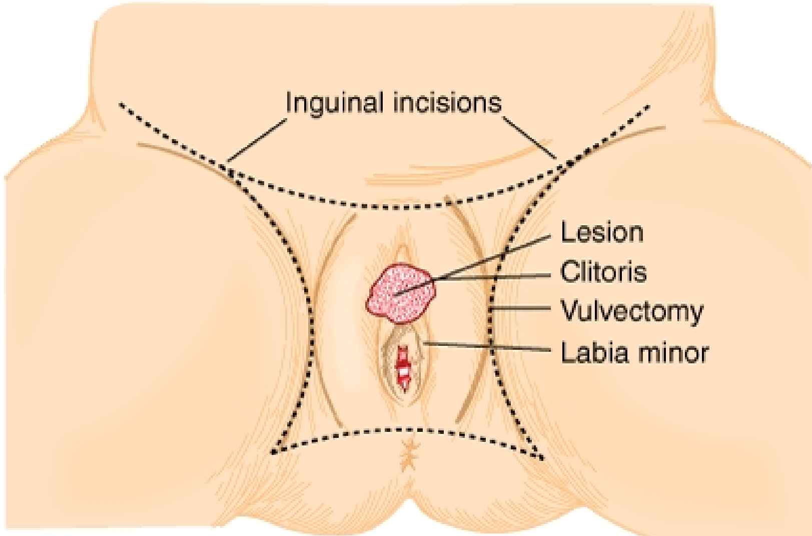
TREATMENT

Surgical Procedures

Procedures in the treatment of invasive vulvar neoplasia include wide local excision, radical partial vulvectomy, and radical complete vulvectomy, and each is described below (Fig. 31-5). Lymphadenectomy may accompany these procedures and typically includes excision of the deep and superficial inguinal lymph nodes (see Fig. 38-29). In certain cases, pelvic lymph nodes also may be excised.

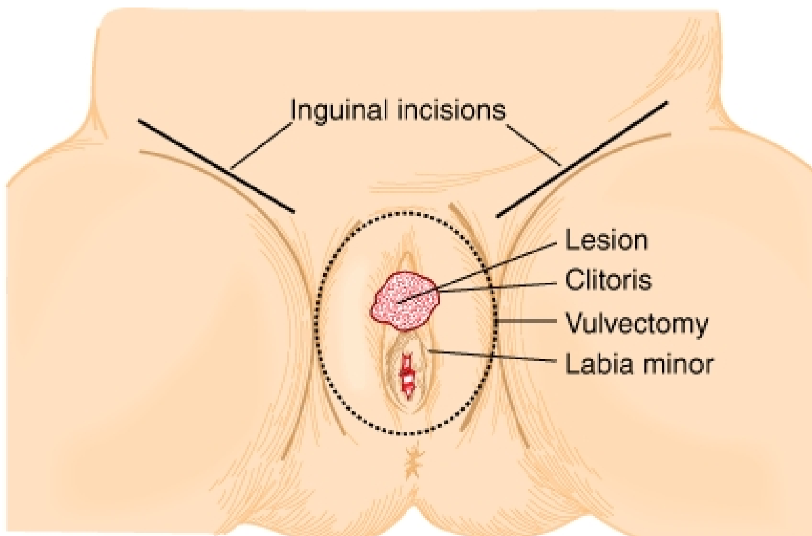
FIGURE 31-5

A

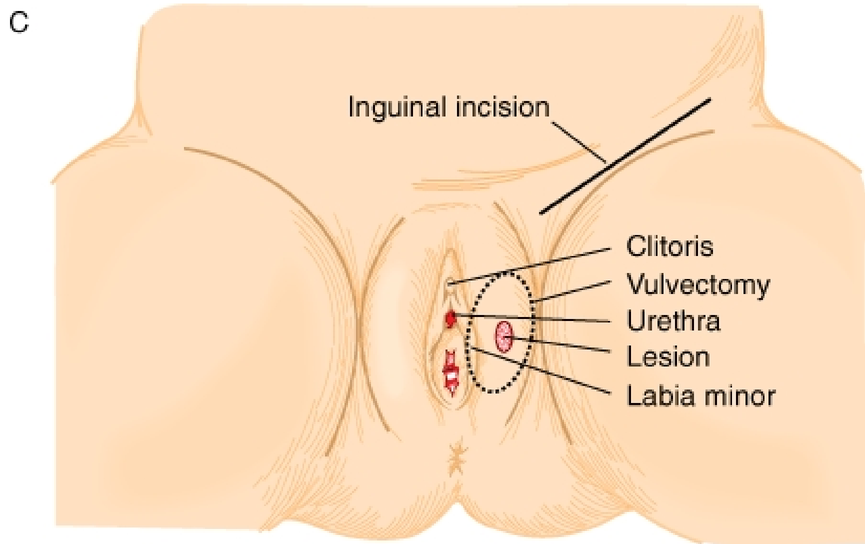


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

B



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Types of vulvectomy used in the treatment of vulvar cancer. **A.** En bloc radical vulvectomy with bilateral inguinal lymphadenectomy. **B.** Radical complete vulvectomy with bilateral inguinal lymphadenectomy. **C.** Radical partial vulvectomy with ipsilateral inguinal lymphadenectomy.

In contrast, the term *skinning vulvectomy* refers to removal of only the skin and superficial subcutaneous tissue. This surgery plays no role in the treatment of invasive vulvar cancer but may be used in noninvasive disease such as cases with widespread multifocal VIN 3 (see Section 43-25, Skinning Vulvectomy).

Microinvasive Tumors

Most women with microinvasive stage IA tumors tend to be younger and have multifocal disease associated with HPV. For curative resection, these patients can undergo *wide local excision,* also termed *simple partial vulvectomy,* to obtain 1- to 2-cm surgical margins around the lesion with dissection down to the superficial fascia of the urogenital diaphragm (see Fig. 38-28). Lymphadenectomy is not indicated for these very low-risk patients.

Early-Stage Vulvar Cancers

RADICAL VULVECTOMY

Women with stage IB and II vulvar cancers and a few stage III resectable vulvar cancers require radical resection of the primary tumor (Fig. 31-6).

FIGURE 31-6

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photograph of invasive vulvar cancer. The lesion seen involves the labia minora bilaterally, urethral orifice, anterior lower vagina, and abuts the clitoris. *(Courtesy of Drs. David Miller and Jayanthi Lea.)*

An en bloc total *radical vulvectomy* involves excision of vulvar tissue between the labiocrural folds, from the perineal body to the superior border of the mons pubis. Dissection is carried downward to the level of the *perineal membrane,* which previously was termed the *deep fascia of the urogenital diaphragm* (see Chap. 38, Perineal Membrane). Conceptually, the rationale behind radical en bloc "butterfly" resection is to excise three areasâ€”the vulvar lesion, the superficial and deep inguinal lymph nodes, and the lymphatics in betweenâ€”to remove all possible "cancer-infiltrated" tissues. Accordingly, the incision includes the inguinal regions to allow lymphadenectomy of the deep and superficial inguinal lymph nodes with transposition of the sartorius muscle. The intent of resection is to obtain clear surgical margins with resulting long-term survival rates of 80 to 90 percent.

However, this approach often removes large pieces of healthy tissue and results in severe perineal disfuguration for a sometimes small, localized vulvar lesion. In addition, long hospital stays and high immediate- and long-term morbidities are common.

Although associated with improved survival, this extensive procedure and the need for complete lymphadenectomy during staging have been reevaluated over the years. Careful histologic review of the skin that bridges the vulva and groins and recent lymph node radiolabeling studies have lead to a more conservative approach to vulvar cancer surgery discussed below.

RADICAL PARTIAL VULVECTOMY

Currently, modified surgical resection of a primary tumor, termed *radical partial vulvectomy,* aims to obtain clear surgical margins of 1 to 2 cm around the tumor, remove all tissue beneath this margin down to the perineal membrane, but avoid excision of other healthy tissues (see Section 43-22, Radical Partial Vulvectomy). This approach often allows preservation of function and significantly less morbidity. Various names have been used to describe this procedure and include *radical local excision, radical wide excision, radical hemivulvectomy,* and *modified vulvectomy.* Inguinal lymphadenectomy is performed using small, separate incisions below and parallel to the inguinal ligament.

RADICAL COMPLETE VULVECTOMY

In a *radical complete vulvectomy* , the entire vulva is removed. The borders of resection are generally the mons pubis superiorly, the perineal body inferiorly, and the labiocrural folds laterally. The clitoris is removed, and the deep margin is extended to the perineal membrane (see Section 43-23, Radical Complete Vulvectomy). This procedure is rarely used in early-stage vulvar cancers.

LYMPHADENECTOMY

The decision to remove superficial and deep inguinal lymph nodes is debatable. In 1979, DiSaia and colleagues reported on reduced excision around the central tumor and selective removal of the superficial nodes. Deep inguinal nodes were removed only if the superficial nodes were positive for metastatic disease. Unfortunately, leaving deep inguinal nodes was associated with nodal recurrences in 5 percent of patients long before the appearance of a central recurrence (Burke, 1995; Stehman, 1992, 1996.)

A modified approach to superficial and deep inguinal lymphadenectomy is performed by preserving the fascia lata. The saphenous vein is also spared in most women. Deep nodes are removed medial to the femoral vein within the opening of the fossa ovalis (Bell, 2000). This procedure has been shown to have comparable recurrence rates to those obtained with classic groin dissection in which fascia lata is removed and the sartorius muscle is transposed over the femoral vessels (Bell, 2000; Hacker, 1983). Complications of wound breakdown, infection, and lymphedema are decreased significantly with this conservative approach (Table 31-4). Steps of lymphadenectomy are described and illustrated in Section 43-24, Inguinal Lymphadenectomy.

Table 31-4 Postoperative Complications

Complication	No. of Events	Percent of Groins
Lymphedema	13	14.0
Lymphocele	11	11.8
Groin infection	7	7.5
Groin necrosis	2	2.2
Groin separation	7	7.5

From Bell, 2000, with permission.

SENTINEL NODE BIOPSY

Recent developments in the management of other malignancies such as carcinoma of the breast suggest that selective dissection of a solitary node or nodes, termed *sentinel node biopsy,* may reduce morbidity and yet adequately assess nodal involvement. The first lymph node to receive lymphatic drainage from the tumor site, termed the *sentinel lymph node,* is considered the first site of malignant lymphatic spread. Therefore, a sentinel lymph node devoid of disease implies the absence of lymph node metastases in the entire draining basin. At present, the Gynecologic Oncology Group (GOG) is conducting a multicenter trial to evaluate the benefit of sentinel node biopsy for vulvar cancer.

Although sentinel node biopsy may decrease postoperative morbidity, clinicians should realize that many women may select procedures with increased morbidity, if they offer a lower cancer recurrence risk. A recent survey in a group of vulvar cancer survivors indicated that although many suffered from cellulitis or severe lymphedema, 60 percent preferred formal superficial and deep inguinal lymphadenectomy to a 5-percent false-negative rate associated with minimally invasive sentinel node procedures.

Node-Positive Cancers

An optimal strategy to manage patients with node-positive vulva cancer is yet to be defined. Several options are available for women who are found to have positive nodes on an ipsilateral groin dissection. One approach is to perform a contralateral inguinal femoral lymphadenectomy. Postoperative irradiation is given to groin and pelvis of the ipsilateral side and contraleral side only if more than one microscopic node is identified. The alternative approach is to limit the dissection to the ipsilateral groin and add postoperative irradiation.

The GOG has established evidence that adjunctive radiation improves survival in patients with positive groin nodes (Homesley, 1986). Two major poor prognostic factors were clinically suspicious or fixed ulcerated groin nodes and two or more positive groin nodes. However, for women with only one positive groin node, survival following radiation does not appear improved compared with lymphadenectomy alone.

CHEMORADIATION

Successful use of chemoradiation for certain cervical cancers suggests that concurrent chemotherapy with radiation in women with vulvar cancer also may improve survival. The GOG is currently conducting a randomized study exploring concurrent chemotherapy in the form of weekly cisplatin with adjuvant postoperative radiation therapy to the inguinopelvic regions to improve inguinopelvic control and survival.

Stage III and IV Cancers

By definition, stage III and IVA vulvar cancers involve adjacent mucosal structures or inguinal lymph nodes. A few advanced-stage vulvar cancers can be treated with primary surgery in the form of a radical partial vulvectomy, adhering to the principle of radical resection to the perineal membrane and obtaining 1- to 2-cm margins. However, most advanced-stage vulvar cancers require resection using some variations of pelvic exenteration and radical vulvectomy.

Recent therapeutic efforts, however, have focused on treatment modalities that combine radiation, chemotherapy, and less aggressive surgery. Phase II studies have demonstrated that primary chemoradiation reduced the necessity of radical surgery or exenteration significantly in patients with advanced vulvar cancer (Moore, 1998). In cases in which a patient does not have fixed groin nodes, pretreatment inguinofemoral lymph node dissection may help determine the need for groin irradiation. Women with negative groin lymph nodes receive radiation therapy to the vulva. All patients with grossly or histologically positive nodes receive radiation therapy to the inguinofemoral and lower pelvic lymph nodes at the discretion of the treating physician.

Although occasional cures have been described for patients with stage IVB disease, most treatment of such patients should be considered palliative.

SURVEILLANCE

Completing primary treatment, all patients receive a thorough physical examination, including a node survey and pelvic examination, every 3 months for the first 3 years. Surveillance examinations then are scheduled every 6 months for the next 2 years. Five years after primary treatment, disease-free patients may be seen annually. Vulvoscopy and biopsies are performed if areas of concern are noted during history or physical examination. Radiologic imaging and biopsies to diagnose possible tumor recurrence are performed as indicated.

RECURRENT DISEASE

In a patient who presents with a suspected recurrence, a careful evaluation should be completed to define the extent of disease. For local vulvar recurrences, surgery is preferred. Typically, a radical partial vulvectomy is performed for treatment of a local recurrence not involving the urethra or perineum. If needed, flap reconstruction of a surgical defect can be completed. For large central recurrences involving the urethra, vagina, or rectum, a total pelvic exenteration may be required. To maintain sexual function, vaginal reconstruction can be completed at the time of surgery or after a short postoperative interval.

For all these procedures, high postoperative morbidity has been reported, and women must be in overall good health to undergo these procedures. For previously irradiated patients who present with gross recurrence, surgery is not a treatment option because of the extraordinary high incidence of operative morbidities and poor prognosis. For patients without prior radiation treatment who refuse surgery or those who are not surgical candidates, external-beam radiation combined with interstitial brachytherapy can be used (see Chap. 28, External Radiation Therapy).

After surgical treatment of local recurrence, if surgical margins are positive for microscopic invasion or metastases are present in the inguinal lymph nodes, then external-beam radiation may have some benefit in those who have not received radiotherapy before. Inguinal lymph node recurrences, however, offer a dismal prognosis. Few of these women are alive at the end of the first

year following diagnosis.

Palliative chemotherapy can be offered to patients with pelvic or distant metastases. However, there are few data to indicate that chemotherapy provides an effective palliative intervention. Only doxorubicin and bleomycin appear to have reproducible activity as single agents. Combination chemotherapy including cisplatin also has shown to have modest activity in recurrent vulvar cancers (Cunningham, 1997; Moore, 1998).

MANAGEMENT DURING PREGNANCY

Squamous cell cancer of the vulva diagnosed and treated surgically during pregnancy is rare, and an incidence of 1 in 20,000 deliveries has been reported (DiSaia, 1997). Nevertheless, all suspicious lesions should be examined and biopsied, even during pregnancy, to prevent a delayed diagnosis.

Radical partial vulvectomy and bilateral groin dissection can be performed when indicated after the eighteenth week of gestation. When diagnosed during the third trimester, lesions may be removed by wide local excision, and definitive surgery can be postponed until the postpartum period. In women in whom diagnosis is not made until delivery, definitive surgery should be started as soon as deemed appropriate by the treating physician.

The mode of delivery is left to the discretion of the obstetrician and is heavily influenced by the state of the postoperative vulva. In instances of vaginal stenosis, significant fibrosis, or tumor involvement, a cesarean delivery is recommended.

MELANOMA

Melanoma of the vulva is the second most common malignancy arising within the vulva. Vulvar melanoma is a disease of the elderly, and its incidence peaks in the fifth to eighth decades of life (Piura, 1992; Podratz, 1983). It develops more commonly among Caucasians than among African-American, Asian, or other more heavily pigmented races (Evans, 1994; Franklin, 1991; Jaramillo, 1985; Piura, 1992; Ronan, 1990).

Malignant vulvar melanoma will arise most commonly from the labia minora, labia majora, or clitoris (Ariel, 1981; Blessing, 1991; Moore, 1998; Piura, 1992; Woolcott, 1988) (Fig. 31-7). Similarly, a variety of benign pigmented lesions including lentigo simplex, vulvar melanosis, acanthosis nigricans, seborrheic keratosis, and junctional, compound, intradermal, or dysplastic nevi, also may be found in these areas (see Chap. 4, Lesions of Pigmentation). In addition, pigmented vulvar neoplasia may include VIN, squamous carcinoma, and Paget disease. Thus, tissue sampling is necessary, and immunohistochemical studies and electron microscopy may help to clarify the diagnosis. Three histologic subtypes of vulvar melanoma have been described: superficial spreading melanoma (SS), nodular melanoma (NM), and acral lentiginous melanoma (AL).

FIGURE 31-7

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photograph of melanoma. *(Courtesy of Dr. Amit Pandya.)*

Vulvar melanomas have been staged by a variety of microstaging systems, including the Chung, the Clark, and the Breslow systems (Table 31-5). The Clark system of staging cutaneous melanomas is based on depth of invasion. Agreeing that depth of invasion is important, Breslow published an alternative list of prognostic indicators but added tumor size and used tumor thickness as the most significant measures. Both the Clark and the Breslow systems have been found to correlate with prognosis in patients with cutaneous melanoma.

Table 31-5 FIGO Staging for Vulvar Melanoma	
FIGO Stage	**Description**
	Primary tumor cannot be assessed
	No evidence of primary tumor
0	Carcinoma in situ (preinvasive carcinoma)
I	Tumor confined to vulva or vulva and perineum, 2 cm or less in greatest dimension
IA	Tumor confined to vulva or vulva and perineum, 2 cm or less in greatest dimension and with stromal invasion no greater than 1.0 mm
IB	Tumor confined to vulva or vulva and perineum, 2 cm or less in greatest dimension and with stromal invasion greater than 1.0 mm
II	Tumor confined to the vulva or vulva and perineum, more than 2 cm in greatest dimension
III	Tumor invades any of the following: lower urethra, vagina, anus
IV	
IVA	Tumor invades bladder mucosa, rectal mucosa, or upper urethral mucosa or is fixed to bone
IVB	Any distant metastasis including pelvic lymph nodes

From Irvin, 2001, with permission.

There are no prospective data from randomized clinical trials evaluating the ideal extent of surgical margins in women with vulvar melanoma. At our institution, we recommend that patients undergo a radical partial vulvectomy with a 2-cm margin for lesions that are 1 to 4 mm thick and a 1-cm margin if lesion thickness is less than 1 mm.

The incidence of occult inguinal lymph nodes is less than 5 percent for thin melanomas (<1 mm) and greater than 70 percent for thick lesions (>4 mm) (Hoskins, 2000). Accordingly, a minimally invasive evaluation of the inguinal lymph nodes, such as sentinel node biopsy, may be reasonable for patients who have tumor thicknesses between 1 and 4 mm. However, this method of evaluation remains a topic of controversy in the management of melanoma. Previous retrospective studies in cutaneous melanoma have confirmed and disproved the superiority of elective regional node dissection versus sentinel lymph node biopsy in patients with intermediate-thickness melanoma (0.76 to 4.0 mm) (Balch, 1982; Milton, 1982; Reintgen, 1983). The appeal of the sentinel node biopsy is based on the possibility of sparing patients with no sentinel node disease the morbidity of a full groin node dissection.

In a GOG study examining the management of vulvar melanoma, the authors were unable to reach a conclusion relative to the benefit of elective lymph node dissection in these patients (Phillips, 1994). Patients with lesions thicker than 4 mm may undergo an elective lymphadenectomy.

Recent trials have suggested that adjuvant therapy may be of benefit in preventing recurrence in certain patients with cutaneous melanoma involving other body surfaces. Specifically, high-dose adjuvant interferon-alpha has been shown to increase both progression-free and overall survival rates in patients with cutaneous melanoma. However, given the small number of women with vulvar melanoma, no trials have yet evaluated the benefit of adjuvant therapy in these women. Moreover, tolerability of the interferon regimen has remained a barrier to patient acceptance.

In general, vulvar melanomas carry a poor prognosis and show a tendency to recur locally and develop distant metastases through hematogenous dissemination. Deaths from vulvar melanoma result more commonly from the effects of widespread metastatic disease, most commonly involving the lungs, liver, or brain. Women diagnosed with vulvar melanoma have a median survival of 61 months. The 5-year survival rate is 60 percent and at 10 years, there is a 50-percent adjusted survival rate (Irvin, 2001). African-American race and increasing age are both significant independent predictors of decreased survival (Irvin, 2001).

BASAL CELL CARCINOMA

Basal cell carcinoma (BCC) of the vulva accounts for less than 2 percent of all vulvar cancers and is found most commonly in elderly women (DiSaia, 1997). In the vulvar area, BCC is characterized by poor pigmentation, pruritus, and a clinical appearance often mimicking other dermatopathologies such as eczema, psoriasis, or intertrigo. As a result, correct diagnosis often is delayed and typically follows treatment for other presumed inflammatory or infectious dermatoses.

Although ultraviolet radiation is thought to be the primary risk factor for BCC on sun-exposed areas, its development on areas protected from sunlight raises the possibility of other, yet undefined etiologic agents. The literature suggests that local trauma and advancing age may contribute to the development of BCC in these sites (LeSueur, 2003; Wermuth, 1970).

BCC should be removed by wide local excision using a minimum surgical margin of 1 cm. Lymphatic or distant spread is rare, However, local recurrences may occur, particularly in tumors removed with suboptimal resection margins.

VULVAR SARCOMA

Sarcoma of the vulva is rare. Leiomyosarcoma, malignant fibrous histiocytoma, epithelioid sarcoma, and malignant rhabdoid tumor are some of the more commonly encountered histologic types. Tumors typically develop as isolated masses in the labia majora, clitoris, or Bartholin gland.

Unlike in squamous cell carcinoma of the vulva, the age of affected women is significantly broader and varies among histologic types. There are no large prospective series reporting the management of vulvar sarcoma, although recommended treatment for most types is primary surgery followed by adjuvant radiation or chemotherapy or both.

BARTHOLIN GLAND ADENOCARCINOMA

Adenocarcinoma of the Bartholin gland accounts for 1 percent of vulvar malignancies, and its incidence peaks in women in their midsixties. Soft, distensible tissue surrounds these tumors, and they may reach considerable size before women develop symptoms. Dyspareunia is a common first complaint.

Bartholin gland infections decrease with advancing age. Thus, Bartholin gland enlargement in a postmenopausal woman should prompt biopsy to exclude malignancy. Solid masses may require fine-needle aspiration to establish a diagnosis. Cystic masses should be drained and suspicious regions of the cyst wall biopsied.

Bartholin gland adenocarcinomas have a tendency to spread into the ischiorectal fossa and can have a propensity for lymphatic spread into the inguinal nodes and pelvic nodes. Therapy includes radical partial vulvectomy with inguinal lymphadenectomy.

VULVAR PAGET DISEASE

Vulvar Paget disease is a heterogeneous group of intraepithelial neoplasias that present similarly as eczematoid, red, weeping areas on the vulva. They often are localized to the labia majora, perineal body, or clitoral area. This disease typically develops in older Caucasian women and accounts for approximately 2 percent of all vulvar tumors. Vulvar Paget disease is accompanied by invasive adenocarcinoma in 10 to 20 percent of cases (Hoskins, 2000). In addition, 20 to 30 percent of patients will have or will later develop an adenocarcinoma at another nonvulvar location.

A histologic classification proposed by Williamson and Brown includes: (1) primary vulvar cutaneous Paget disease, (2) Paget disease as an extension of an associated adjacent primary cancer such vulvar, anal, or rectal cancer, and (3) Paget disease as an extension of transitional cell carcinoma of the bladder or urethra. The histologic differentiation of the types of Paget disease is of utmost importance because the specific diagnosis has significant influence on the treatment provided.

Primary cutaneous vulvar Paget disease displays slow growth. Thus, with invasion of 1 mm or less, there is little risk for recurrence. These lesions can be treated with a wide local excision. However, if invasive disease is suspected, a radical partial vulvectomy is warranted. Screening and surveillance for tumors at nongynecologic sites should be considered for all patients with Paget disease.

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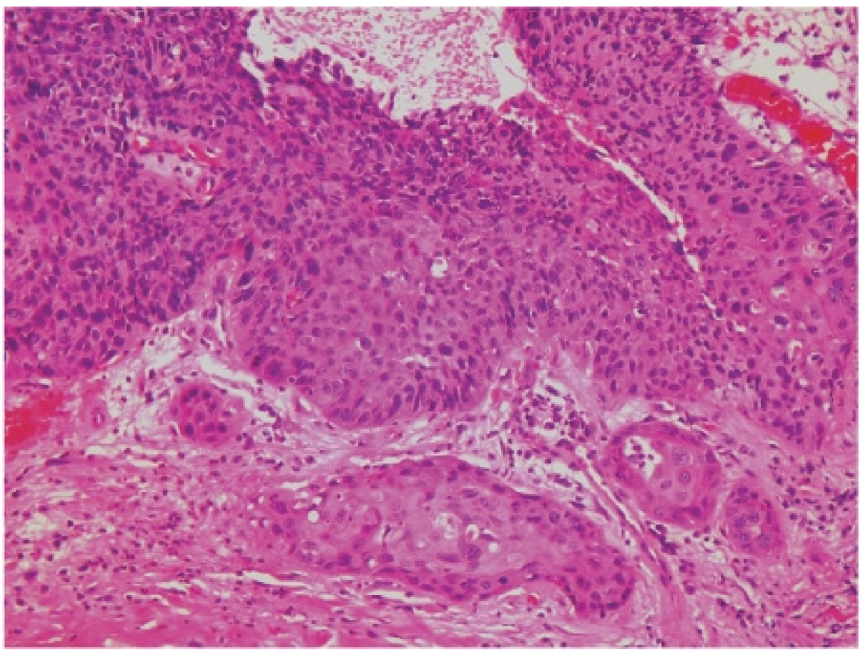
VAGINAL CANCER: INTRODUCTION

Primary vaginal carcinoma is rare and comprises only 1 to 2 percent of all gynecologic malignancies (Creasman, 1998; Pride, 1977). This low incidence reflects the infrequency at which primary carcinoma arises in the vagina as well as the strict criteria for its diagnosis. According to International Federation of Gynecology and Obstetrics (FIGO) staging criteria, a lesion in the vagina that involves adjacent organs such as the cervix or vulva is, by convention, deemed primary cervical or vulvar, respectively (Pecorelli, 1999). The most common histologic type of primary vaginal cancer is squamous cell carcinoma, followed by adenocarcinoma (Fig. 32-1) (Platz, 1995).

FIGURE 32-1



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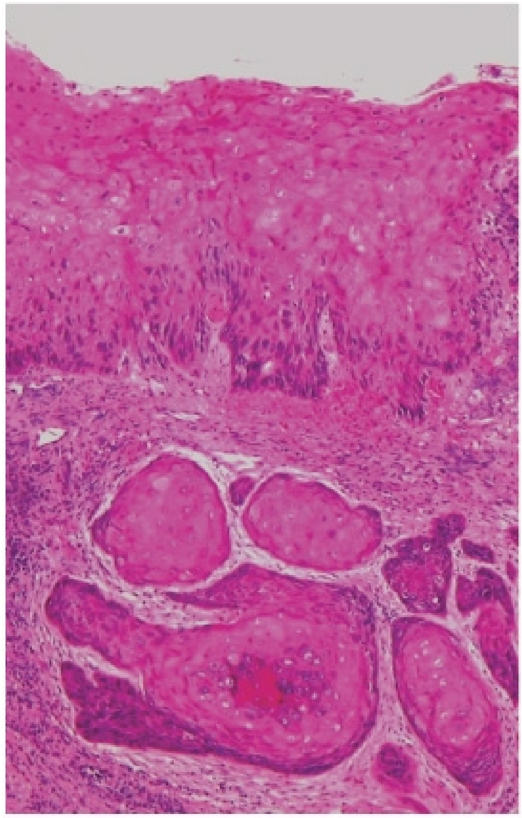

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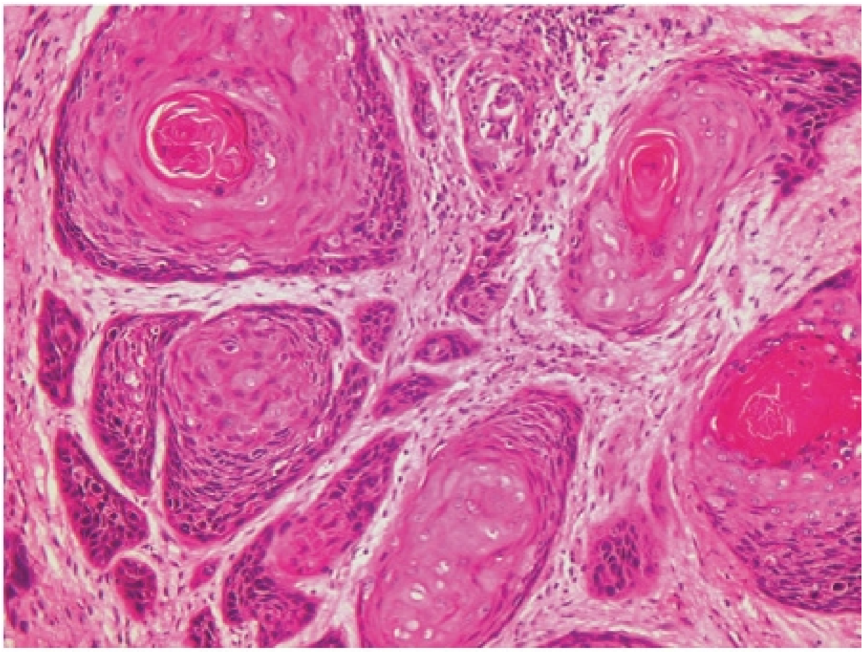

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Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Sections showing invasive squamous cell carcinoma of the vagina. **A.** Superficially invasive squamous cell carcinoma of the vagina with overlying squamous cell carcinoma in situ (× 10). **B.** Invasive, well-differentiated squamous cell carcinoma of the vagina (× 4). **C.** Invasive, well-differentiated squamous cell carcinoma of the vagina (× 10). Invasive tumor is composed of irregular nests of malignant squamous cells with keratin pearls and intercellular bridges. *(Courtesy of Dr. Kelley Carrick.)*

ANATOMY

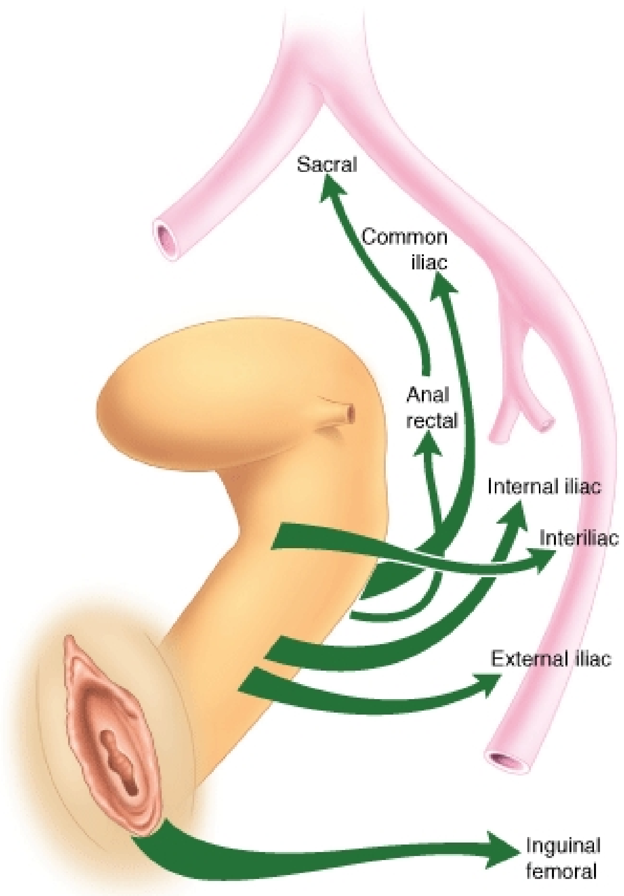
Vaginal Epithelium

Embryologically, both the mÃ¼llerian ducts and the urogenital sinus contribute to form the vagina (see Fig. 18-4). Early in fetal development, the caudal ends of the mÃ¼llerian ducts fuse to form the uterovaginal canal, which is lined by columnar epithelium. Subsequently, squamous cells from the urogenital sinus migrate along the uterovaginal canal and replace this original columnar epithelium. These squamous cells stratify, and the vagina begins to mature and thicken (Zaino, 2002). Underlying this epithelium, muscularis and adventitial layers are found (see Fig. 24-5).

Vascular and Lymphatic Supply

Local extension and lymphatic invasion are common patterns of vaginal cancer spread. The lymphatic channels that drain the vagina form extensive, complex, and variable anastamoses (Fig. 32-2). As a result, any node in the pelvis, groin, or anorectal area may drain any part of the vagina (Zaino, 2002). However, the external, internal, and common iliac lymph nodes are the primary sites of vaginal lymphatic drainage. Alternatively, the posterior vagina may drain to the inferior gluteal, presacral, or perirectal lymph nodes, and the distal third of the vagina may drain to the superficial and deep inguinal lymph nodes (Frank, 2005).

FIGURE 32-2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Lymphatic drainage patterns of the vagina. (From Stenchever, 2001, with permission.)

Hematogenous spread of vaginal cancer is less frequent, and venous drainage consists of the uterine, pudendal, and rectal veins, which drain into the internal iliac vein. Arterial blood supply to the vagina comes primarily from branches of the internal iliac artery, which include the uterine, vaginal, middle rectal, and internal pudendal arteries (see Fig. 38-22).

SQUAMOUS CELL CARCINOMA

Incidence

Squamous cell carcinoma accounts for 70 to 80 percent of all primary vaginal cancers (Beller, 2003; Platz, 1995). Its incidence is 0.42 per 100,000 in white women and 0.93 per 100,000 in black women. This has not changed significantly in the last 30 years (Cramer, 1974; Platz, 1995).

Risks

As with other cancers of the lower reproductive tract, the human papillomavirus (HPV) has been closely linked with squamous cell vaginal cancer (see Chap. 29, Human Papillomavirus). For example, Daling and colleagues (2002) analyzed results from a case-control study of 156 women with squamous cell carcinoma in situ or invasive vaginal carcinoma. Human papillomavirus DNA was detected in 82 percent of the in situ lesions and 64 percent of the invasive tumors. Specifically, antibodies to HPV serotypes 16 and 18 were identified in more than 50 percent of all patients. Because of this association with HPV infection, vaginal in situ and invasive squamous cell carcinoma share risk factors similar to cervical cancer, which include five or more lifetime sexual partners, early age at first intercourse, and current cigarette smoking.

DIAGNOSIS

Vaginal bleeding is the most common complaint associated with vaginal cancer, although pelvic pain and vaginal discharge also may be noted. Less frequently, lesions involving the anterior vaginal wall may lead to dysuria, hematuria, or urgency. Alternatively, constipation may result from those of the posterior wall. Most vaginal cancers develop in the upper third of the vagina. Moreover, of those with cancers, women who had a prior hysterectomy are significantly more likely to have lesions in the upper vagina (70 percent) than those without prior hysterectomy (36 percent) (Chyle, 1996).

During pelvic evaluation in all women, the vagina should be inspected as the speculum is being inserted or removed. If a gross lesion is found, vaginal cancer usually can be diagnosed following punch biopsy in the office. Biopsy may be obtained with a Tischler biopsy forceps, (see Fig. 29-11). An Emmett hook may be used to elevate and stabilize vaginal tissue during biopsy. If a gross lesion is not detectable, vaginoscopy can be useful to direct biopsies, as described in Chapter 29, Vaginal Colposcopy. Bimanual examination can assist in determining the tumor size, and rectovaginal examination is especially important for posterior wall lesions.

Once cancer is diagnosed, no specific laboratory testing other than that used generally for preoperative preparation, such as complete blood count and serum chemistry panel, is required. Computed tomographic (CT) scanning can delineate the size and extent of many tumors (Fig. 32-3). However, if the extent of cancer expansion is unclear, magnetic resonance (MR) imaging is the most useful imaging tool available to visualize the vagina. Proctosigmoidoscopy to a depth of at least 15 cm can be helpful to detect local bowel invasion, whereas cystourethroscopy should be performed in the presence of anterior tumors to exclude bladder or urethral involvement.

FIGURE 32-3

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Computed tomography (CT) scan reveals size and extent of vaginal mass (arrow). (*Courtesy of Dr. Betty Chen.*)

STAGING AND CLASSIFICATION

Staging of vaginal cancer is similar to that for cervical cancer and is completed clinically by physical examination and with the assistance of cystourethroscopy, proctosigmoidoscopy, and chest radiography (Table 32-1). Both CT scanning and MR imaging may be useful in treatment planning but are not used to determine disease stage.

Table 32-1 Vaginal Cancer Evaluation
Vaginal biopsy
Physical examination
Endocervical curettage
Endometrial biopsy
Cystourethroscopy
Proctosigmoidoscopy
Chest radiograph
Abdominal/pelvic CT scan or MR imaging[a]

CT = computed tomographic; MR = magnetic resonance.

[a] Useful for treatment planning but not used to assign FIGO stage.

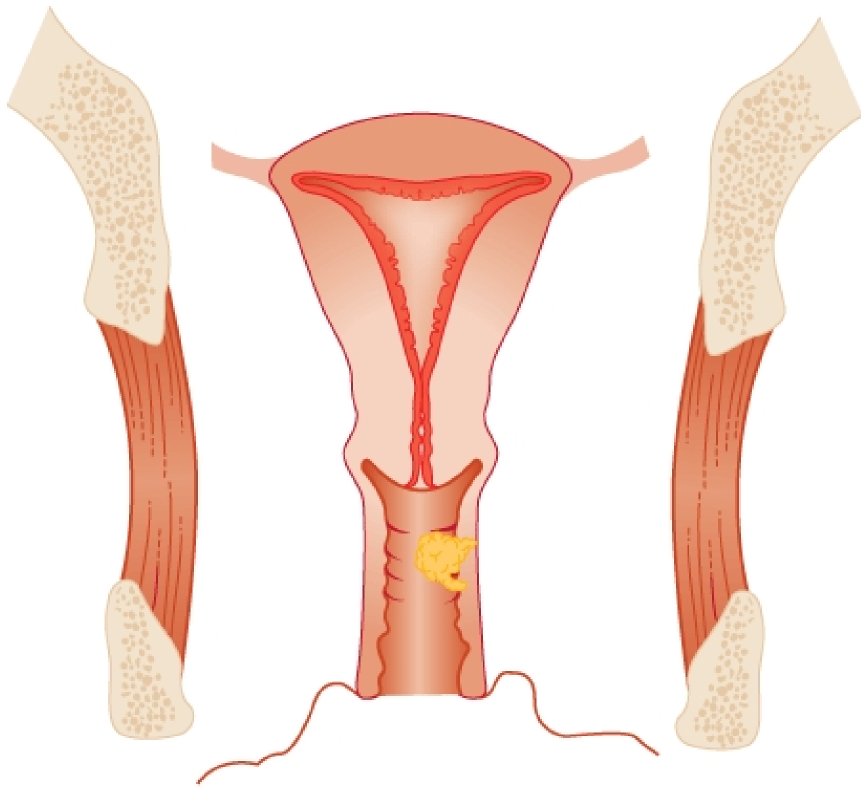
PROGNOSIS

The prognosis of squamous cell carcinoma of the vagina has improved since the 1950s. At that time, Palmer published a review of 992 cases, which showed a dismal 5-year survival rate of only 18 percent. Advances in radiation technology and earlier diagnosis

are largely responsible for the improved 5-year survival rate. Currently, this rate ranges from 45 to 60 percent for all stages (Frank, 2005; Hellman, 2006).

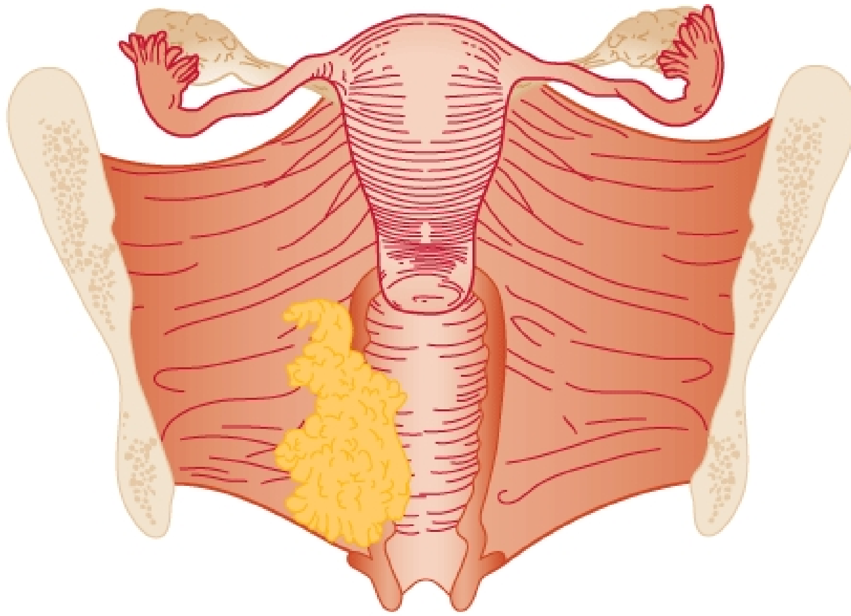
The prognosis of squamous cell carcinoma of the vagina depends primarily on FIGO stage (Fig. 32-4 and Table 32-2) (Frank, 2005; Peters, 1985b). The 5-year disease-specific survival rate is 85 percent for women with stage I disease, 78 percent for those with stage II, and 58 percent for those with stage III or IVA (Fig. 32-5).

FIGURE 32-4

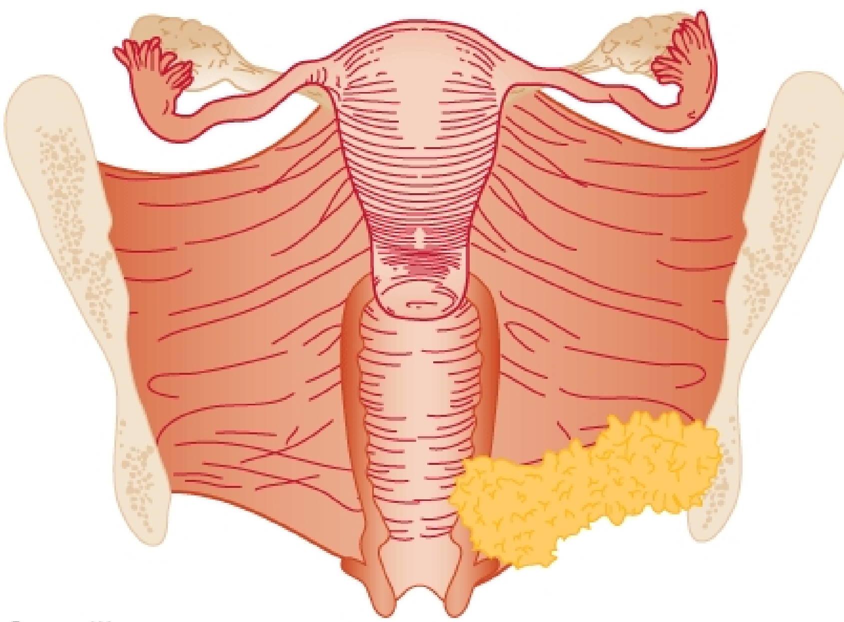


Stage I

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



Stage II.



Stage III.

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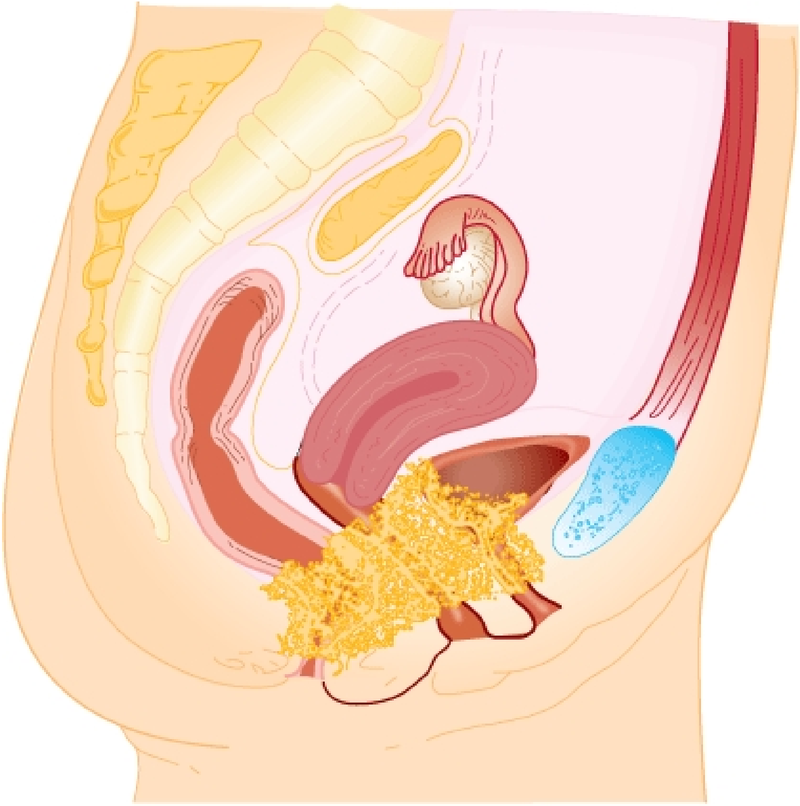
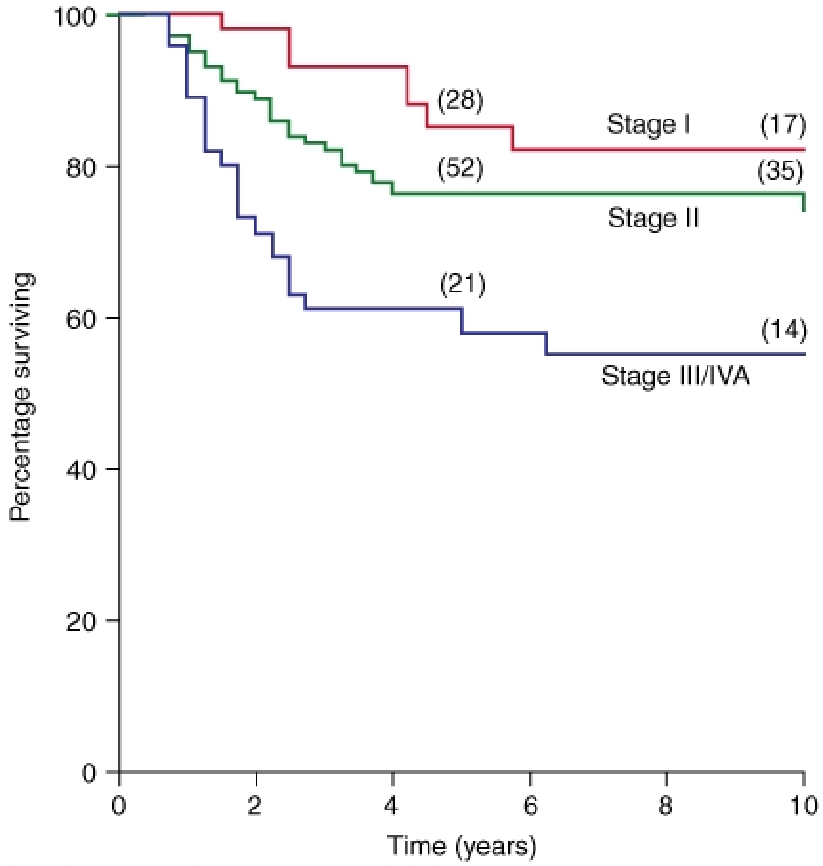


Stage IVA.

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Staging of vaginal cancer.

FIGURE 32-5



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Disease-specific survival by disease stage for 193 women with squamous cell carcinoma of the vagina. Women with stage III and IVA disease were combined for the analysis because of the small number of patients (n = 7) with stage IVA disease. Numbers in parentheses indicate the number of patients at risk 5 or 10 years after treatment. (*From Frank, 2005, with permision.*)

Table 32-2 FIGO Staging Classification of Vaginal Cancer

Stage	Definition
0	Carcinoma in situ, intraepithelial neoplasia
I	The carcinoma is limited to the vaginal wall
II	The carcinoma has involved the subvaginal tissue but has not extended to the pelvic wall
III	The carcinoma has extended to the pelvic wall
IV	The carcinoma has extended beyond the true pelvis or has involved the mucosa of the bladder or rectum; bullous edema as such does not permit a case to be allotted to stage IV
IVA	Tumor invades bladder and/or rectal mucosa and/or direct extension beyond the true pelvis
IVB	Spread to distant organs

FIGO = International Federation of Gynecologic Oncologists.

TREATMENT

Owing to vaginal cancer's rarity, there is a paucity of prospective, randomized trials evaluating its treatment. Therefore, therapy is individualized and based on factors such as tumor type, stage, location, and size.

Stage I

Both surgery and radiotherapy are options for stage I disease. However, surgery is preferred for most if surgical margins negative for cancer can be achieved. A review of the National Cancer Data Base showed that women treated with surgery alone had a significantly improved 5-year survival rate compared with those treated with radiation (90 percent versus 63 percent) (Creasman, 1998). However, others have found no significant difference in disease-free survival rates at 5 years in women treated with surgery compared with radiation alone (Stock, 1995). Radiotherapy may be delivered by external beam or brachytherapy or both as described in Chapter 28, Radiation Therapy. Specifically, brachytherapy alone has been used successfully to treat small stage I lesions (Nori, 1983; Pempree, 1985; Perez, 1999; Reddy, 1991).

Stage II

Stage II disease is treated with either surgery or radiation at the discretion of the treating clinician. Stock and colleagues (1995) found a significant survival advantage at 5 years in those with stage II disease treated with surgery compared with those treated with radiation (62 percent versus 53 percent). Review of the National Cancer Data Base showed that the 5-year survival rate for women with stage II disease treated with surgery alone was 70 percent; with radiotherapy alone 57 percent; and with a combination of surgery and radiotherapy 58 percent (Creasman, 1998). However, other authors have found no survival advantage of surgery compared with radiotherapy in stage II disease (Davis, 1991; Rubin, 1985).

If radiation is to be administered, it is given most often as a combination of external beam radiation and brachytherapy. External beam radiation generally is given first, and depending on tumor response, brachytherapy is tailored to remaining disease. Radiation is recommended when it is felt that negative margins cannot be achieved with surgery owing to the anatomic location or size of the tumor or if a woman has medical comorbidities and is deemed not to be a surgical candidate.

Stage III and IV

For advanced disease, external beam radiation alone or a combination of this and brachytherapy usually is administered (Frank, 2005). Concurrent chemotherapy with cisplatin as a radiation adjunct is recommended (see Chap. 28, Combination of Ionizing Radiation and Chemotherapy).

Chemoradiation

Chemotherapy in combination with radiation treatment has been found to be superior to radiation alone for squamous cell carcinoma of the cervix in a number of prospective, randomized trials (Keys, 1999; Morris, 1999; Peters, 2000; Rose, 1999; Whitney, 1999). Although the numbers of women with vaginal cancer have been too small to make a prospective, randomized trial feasible, it is generally extrapolated that the addition of chemotherapy to radiation treatment would be beneficial in those with vaginal cancer as well. In a small series, it was found that the addition of concurrent chemotherapy allowed a 10 to 33 percent decrease in the total amount of radiation delivered (Dalrymple, 2004). Although the authors were not intending to show an improved survival with chemoradiation, they found that local control of tumor growth and survival rates were comparable with those who had received higher doses of radiation alone. Decreases in the total dose of radiation may lead to lower rates of vaginal stenosis and fistula formation.

Chemotherapy

In general, chemotherapy alone is ineffective in the treatment of vaginal cancer, although data supporting this are limited. The Gynecologic Oncology Group (GOG) performed a phase II trial evaluating cisplatin for advanced or recurrent cancer of the vagina in 26 patients. Only one woman with squamous cell carcinoma achieved a complete response. Five of 16 patients with squamous cell

carcinoma had stable disease, and 10 had progression of disease with cisplatin. From this it was concluded that single-agent cisplatin at that dose was ineffective for treatment of vaginal carcinoma (Thigpen, 1986). To date, this has been the only prospective, randomized trial evaluating chemotherapy alone in vaginal cancer.

Radiation Therapy

Radiation is delivered to the deep and superficial inguinal lymph nodes if biopsy reveals metastasis or prophylactically if the distal third of the vagina is involved. In a retrospective review, Perez and colleagues (1999) found that of 100 women who did not receive groin radiation, if disease was confined to the upper two-thirds of the vagina, then none developed groin metastases. However, if disease involved the lower third or extended throughout the length of the vagina and radiotherapy was not delivered, then groin metastases developed in 3 of 29 (10 percent) and in 1 of 20 patients, respectively.

SURVEILLANCE

Because treatment failures usually occur within 2 years of completion of the primary therapy, patients usually are followed every 3 months for the first 2 years and then every 6 months until 5 years (Pingley, 2000; Rubin, 1985). After 5 years following treatment, women can be seen annually. A Pap smear and pelvic examination with careful attention to the inguinal and scalene nodes are performed. Surveillance imaging with CT scanning or MR imaging is at the clinician's discretion.

RECURRENT DISEASE

Disease recurrence should be confirmed by biopsy if further treatment is planned. Therapeutic options in women with central pelvic recurrence who have had prior pelvic radiation are limited. Pelvic exenteration can be considered if a patient is psychologically and medically fit to undergo radical surgery with high morbidity. Moreover, it should be attempted only in those whose disease is limited to the central pelvis. Therefore, clinicians should be alert to the triad of sciatic pain, leg edema, and hydronephrosis, which is suggestive of pelvic sidewall disease. These women are not surgical candidates but can be managed with chemoradiation or with chemotherapy alone for women previously irradiated.

Survival after relapse is poor. In a review of 301 patients, 5-year survival was 20 percent for local recurrence and 4 percent for metastatic disease recurrence (Chyle, 1996).

SQUAMOUS CELL VAGINAL CANCER IN PREGNANCY

Squamous cell vaginal cancer in pregnancy is rare, and only 13 cases have been reported in the literature (Fujita, 2005). Women may be treated with surgical resection, radiation, chemoradiation, or a combination of these, and survival rates mirror those of nonpregnant women. Typically, treatment and timing of delivery must be tailored to the individual patient because there is limited evidence to support a general recommendation. Women may elect to terminate their pregnancies or effect delivery at the time of cancer diagnosis to begin treatment. However, this does not appear to improve survival rates. Alternatively, a woman may choose to continue her pregnancy, and most who do, undergo cesarean delivery.

VERRUCOUS CARCINOMA

Verrucous carcinomas of the vagina are an extremely rare variant of squamous cell carcinoma. Grossly, verrucous carcinoma is a warty and fungating mass that grows slowly, pushing into rather than invading contiguous structures (Fig. 32-6) (Isaacs, 1976). The diagnosis may be difficult to determine and may not be possible with a superficial biopsy. For this reason, multiple, large biopsies are recommended to avoid misdiagnosis and inadequate treatment.

FIGURE 32-6

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Verrucous carcinoma of the vagina. (*From Zaino, 2002, with permission.*)

Treatment requires surgical resection with either wide local excision for smaller lesions or radical surgery for larger tumors (Crowther, 1988). Verrucous carcinomas are resistant to radiotherapy and actually may transform to conventional squamous cell carcinoma after radiation (Zaino, 2002). Therefore, radiation treatment is contraindicated for these tumors.

Verrucous carcinoma has a tendency for local recurrence but rarely metastasizes to lymph nodes. This cancer may coexist with squamous cell carcinoma. When it does, it should be managed as a squamous cell carcinoma.

VAGINAL ADENOSIS- AND DES-RELATED TUMORS

Vaginal adenosis is a condition common in females exposed to diethylstilbestrol (DES) (see Chap. 18, Acquired Uterine Defects). *Adenosis* found in the vagina is defined as the presence of subepithelial glandular structures lined by mucinous columnar cells that resemble endocervical cells (Sandberg, 1965). These are residual glands of mÃ¼llerian origin. Clinically, adenosis appears as red granular spots or patches and does not stain following Lugol solution application.

Adenocarcinoma

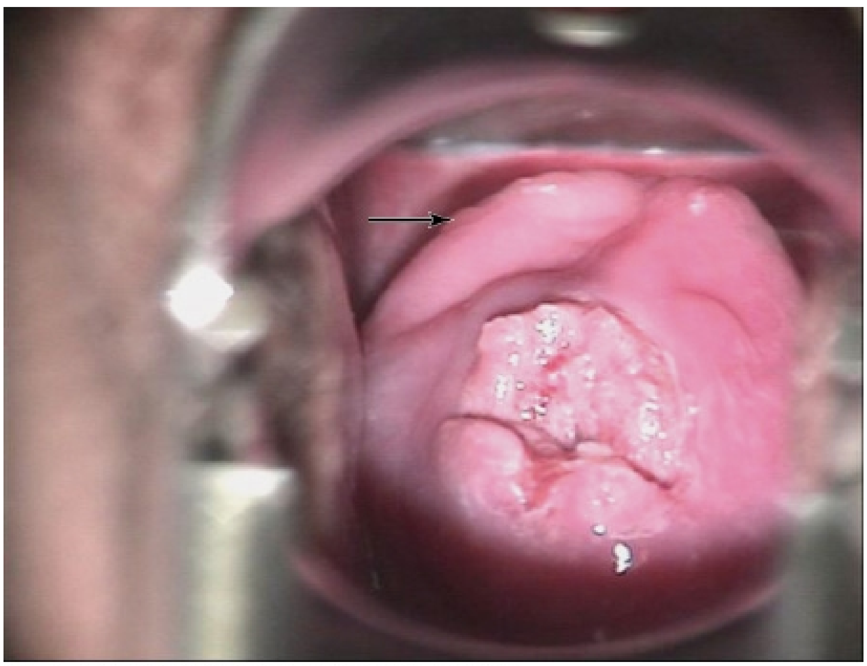
Primary adenocarcinoma of the vagina is rare, comprising only 13 percent of all vaginal cancers (Platz, 1995). When the vagina is the primary site, it is believed to arise from adenosis. More commonly, vaginal adenocarcinoma is metastatic disease, typically from a lesion higher in the genital tract. Metastatic disease frequently arises from the endometrium, although it also may originate in the cervix or ovary (Saitoh, 2005). In addition, adenocarcinoma metastases from the breast, pancreas, kidney, and colon also have been identified in the vagina.

Treatment is similar to that for squamous cell carcinoma, and either surgery, radiation, or a combination of both can be used. Primary adenocarcinoma of the vagina is a more aggressive tumor than squamous cell carcinoma, and in one series of 30 patients, it was associated with greater than twice the local and metastatic relapse rates of squamous cell carcinoma (Chyle, 1996).

Clear Cell Adenocarcinoma

In 1971, clear cell adenocarcinoma of the vagina was linked initially to in utero exposure to DES (Fig. 32-7) (see Chap. 18, Acquired Uterine Defects). It is estimated that 1 to 4 million women used DES and that approximately 0.01 percent of females exposed in utero developed clear cell adenocarcinoma of the vagina (Melnick, 1987). Most DES-exposed patients with vaginal cancer were born between 1951 and 1953, when the drug was prescribed most frequently. The median age at diagnosis of vaginal clear cell carcinoma in the United States is 19 years.

FIGURE 32-7



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photograph of a cervix in a patient with in utero DES exposure. A vaginal shelf, often described as a vaginal hood, is seen above the cervix **(arrow)** . (*Courtesy of Dr. Claudia Werner* .)

However, in the Netherlands, a bimodal distribution of vaginal clear cell carcinoma has been shownâ€”the first peak occurring with a mean age of 26 years and the second at 71 years. The younger group all had been exposed in utero to DES, whereas the older group, born before 1947, had not been exposed (Hanselaar, 1997). It remains to be seen if the incidence of vaginal clear cell carcinoma will rise as the DES-exposed population ages.

Treatment is similar to that for squamous cell carcinoma of the vagina. Five-year survival rates for 219 patients with stage I

disease was 92 percent and was equivalent regardless of mode of therapy (Senekjian, 1987). The reported 5-year survival for 76 patients with stage II disease was 83 percent (Senekjian, 1988).

EMBRYONAL RHABDOMYOSARCOMA (SARCOMA BOTRYOIDES)

Embryonal rhabdomyosarcoma is the most common malignancy of the vagina in infants and children. Most are of the subtype sarcoma botryoides. This rare tumor develops almost exclusively in girls aged younger than 5 years, although vaginal and cervical sarcoma botryoides have been report in females aged 15 to 20 years (Copeland, 1985a).

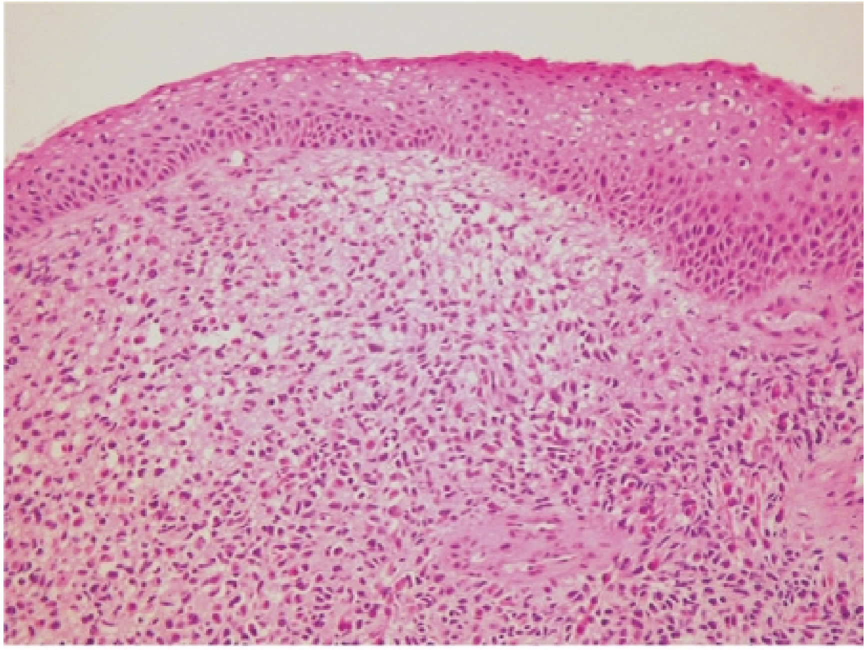
In infants and children, sarcoma botryoides usually is found in the vagina; in reproductive-aged women, within the cervix; and after menopause, within the uterus. Its name, derived from the Greek word *botrys,* which means "bunch of grapes", describes its appearance (Fig. 32-8). The gross specimen can exhibit multiple polyp-like structures or can be a solitary growth with a nodular, cystic, or pedunculated appearance (Hilgers, 1970). Although this distinctive appearance may guide diagnosis, the classic histologic finding of this tumor is the rhabdomyoblast (Fig. 32-9).

FIGURE 32-8

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Sarcoma botryoides protruding through the vaginal introitus. (*From North American Society for Pediatric and Adolescent Gynecology, 2001, with permission.*)

FIGURE 32-9



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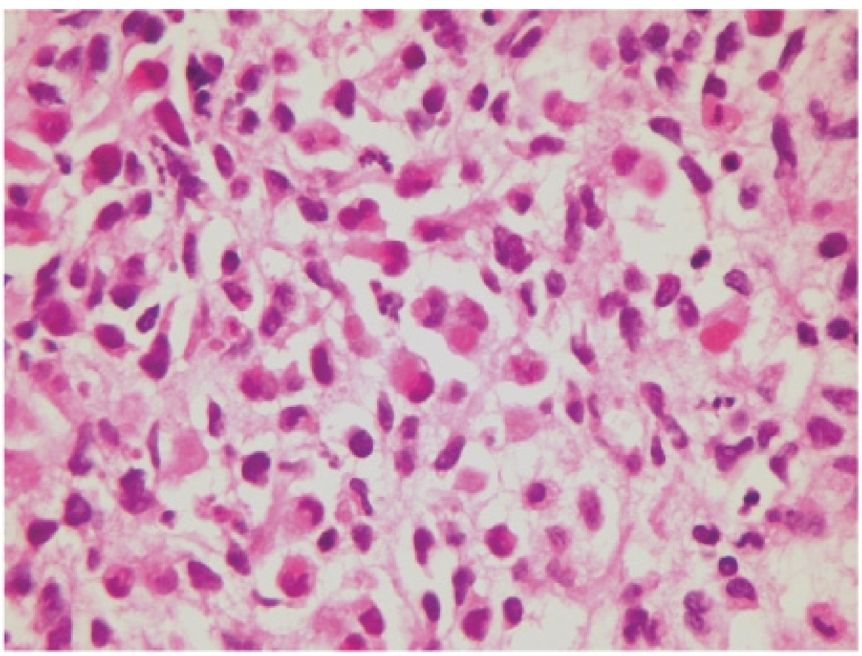

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Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

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A. Embryonal rhabdomyosarcoma, botryoid type (× 10). Malignant embryonal rhabdomyoblasts lie within a fibromyxoid stroma beneath the vaginal epithelium and cluster around blood vessels. **B.** Embryonal rhabdomyosarcoma, botryoid type (× 40). Undifferentiated round and spindled cells, some with brightly eosinophilic granular cytoplasm, are suggestive of rhabdomyoblastic differentiation. (*Courtesy of Dr. Kelley Carrick.*)

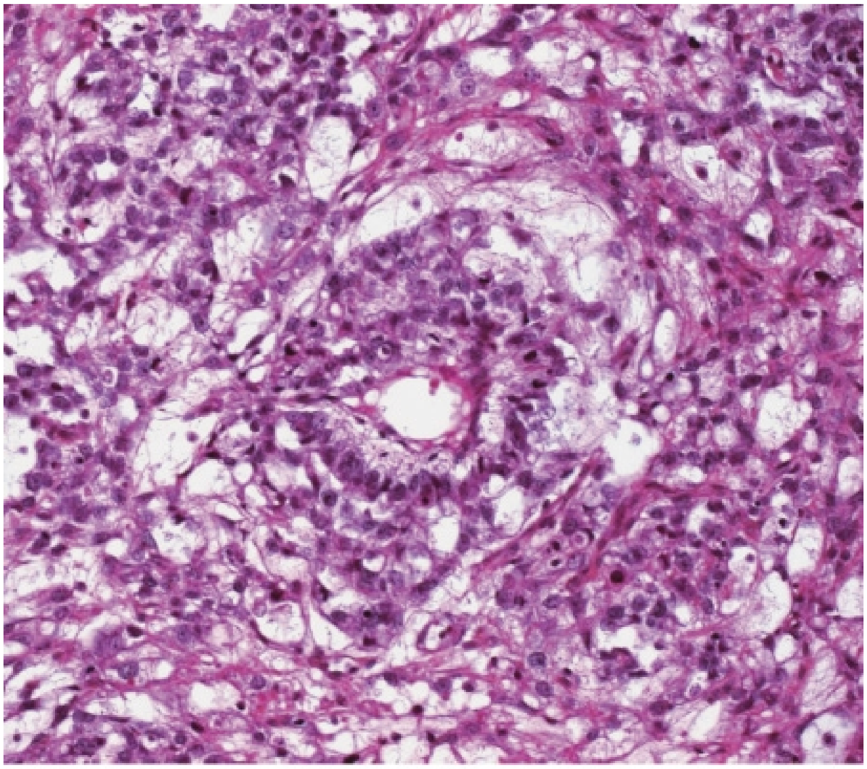
Embryonal rhabdomyosarcomas have a poor prognosis, but sarcoma botryoides is the easiest to treat and has the best chance of cure. It may be that its superficial location allows earlier detection (Copeland, 1985a).

As the result of work by the Intergroup Rhabdomyosarcoma Study (IRS) group, treatment of sarcoma botryoides has undergone dramatic revision. Before 1972, vaginal sarcoma botryoides was treated with pelvic exenteration (Hilgers, 1975). Since that time, four sequential prospective clinical trials to optimize the treatment and survival of childhood rhabdomyosarcoma have been completed. Within this series of four trials, each phase gradually shifted disease management away from radical surgery and toward primary chemotherapy followed by conservative surgery to excise residual tumor (Andrassy, 1995, 1999; Hays, 1981, 1985). In the last trial (IRS-IV), patients underwent primary chemotherapy. All but one patient, who died of chemotherapy-related toxicity, are alive without evidence of disease (Andrassy, 1999). The authors concluded that primary chemotherapy without surgery is adequate for most patients.

YOLK SAC TUMOR (ENDODERMAL SINUS TUMOR)

This type of adenocarcinoma is a germ cell tumor (see Chap. 36, Yolk Sac Tumors). Although most often developing in the gonads, yolk sac tumors rarely may arise in the vagina and usually in children aged 2 years or younger (Young, 1984). The clinical presentation is similar to that of sarcoma botryoides, and the most common symptom is bloody vaginal discharge. Grossly, the tumor differs from sarcoma botryoides, and a yolk sac tumor appears polypoid or sessile and often ulcerated (Young, 1984). On microscopic examination, these tumors most commonly have a reticular pattern. A classic finding, though not always present, is the Schiller-Duval body. This is a papilla with a single central vessel (Fig. 32-10).

FIGURE 32-10



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

The Schiller-Duval body is a glomerulus-like structure with a central blood vessel surrounded by embryonal cells. (*Courtesy of humpath.com.*)

Serum alpha-fetoprotein (AFP) is a useful tumor marker, and a determination should be ordered preoperatively if a yolk sac tumor is suspected. It can be used to monitor response to treatment and to detect disease recurrence before it becomes evident clinically (Copeland, 1985b).

Earlier studies demonstrated success with the chemotherapy regimen vincristine, adriamycin, and cyclophosphamide (VAC) for the treatment of yolk sac tumors (Copeland, 1985b; Young, 1984). More recently, the combination of bleomycin, etoposide, and cisplatin (BEP) has been used with excellent results (Arora, 2002; Handel, 2002; Terenziani, 2007). Neoadjuvant chemotherapy has been used to shrink the tumor and minimize or obviate surgical resection. Yolk sac tumors are responsive to radiation. However, radiotherapy should be used with caution in this age group given the severe side effects, such as loss of reproductive and sexual function, femoral head necrosis, and abnormal pelvic bone growth (Aartsen, 1993; Arora, 2002).

LEIOMYOSARCOMA

Leiomyosarcoma is the most common type of vaginal sarcoma in adults. However, it is estimated to comprise no more than 1 percent of vaginal malignancies, and only 138 cases have been described in the literature to date (Creasman, 1998).

Because of the small number of these tumors, their epidemiology has not been widely studied, and few risk factors have been identified. However, patients previously treated with pelvic radiotherapy for cervical cancer appear to be at risk.

Affected women most often complain of an asymptomatic vaginal mass. However, vaginal, rectal, or bladder pain; bleeding or discharge from the vagina or rectum; dyspareunia; or difficult micturition also may be noted. Any wall of the vagina may be affected, but most tumors develop posteriorly (Ahram, 2006). Microscopically, tumors resemble uterine leiomyosarcoma (see Fig. 34-1). Tumors spread by local invasion and hematogenous dissemination (Zaino, 2002).

Surgical resection with negative margins is the preferred primary treatment. The benefit of adjuvant radiation is unclear owing to a lack of controlled trials, however, some clinicians recommend adjuvant radiation for those with high-grade tumor or local recurrence (Curtin, 1995).

CARCINOSARCOMA (MALIGNANT MIXED MÃ¼LLERIAN TUMOR)

Carcinosarcoma contains both malignant epithelial (carcinomatous) and stromal (sarcomatous) elements. Although most commonly developing in the uterus, it can arise from other sites such as the ovaries or peritoneum. Rarely found in the vagina, these highly aggressive tumors have been described in only eight cases in the literature (Neesham, 1998; Shibata, 2003). Of these eight women, four had received prior pelvic radiation.

Given the rarity of this tumor and the lack of controlled trials, optimal treatment is unknown. Most patients have been treated with surgical resection alone, whereas others have received primary radiotherapy or combined surgery and adjuvant radiation. The 5-year survival rate is reported to be only 17 percent (Peters, 1985a).

MELANOMA

Primary malignant melanoma in the vagina is rare, accounting for less than 3 percent of all vaginal cancers. In women, 1.6 percent of melanomas are genital. The most common site is the vulva (70 percent), followed by the vagina (21 percent) and the cervix (9 percent) (see Chap. 31, Melanoma) (Miner, 2004). Using data from the U.S. National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database, Weinstock (1994) estimated that the incidence of vaginal melanoma is 0.26 per 10,000 women per year. Both U.S. and Swedish studies have shown the mean age at diagnosis to be 66 years (Ragnarsson-Olding, 1993; Reid, 1989).

The most common presenting symptoms include vaginal bleeding, vaginal mass, and vaginal discharge (Gupta, 2002; Reid, 1989). Vaginal melanoma is often detected late, and this may be largely responsible for poor treatment outcomes.

Cutaneous melanomas at other body sites are staged by a variety of microstaging systems, including the Chung, the Clark, and the Breslow systems, which use staging criteria such depth of invasion, tumor size, and tumor thickness. However, Clark levels are not applicable to vaginal melanoma because the typical skin landmarks used are not present. Therefore, staging is based on tumor thickness, as described by Breslow or Chung.

With a reported 5-year survival rate ranging from 10 to 20 percent, the prognosis is among the worst of vaginal malignancies (Beller, 2003; Ragnarsson-Olding, 1993; Signorelli, 2005; Weinstock, 1994). Although survival rates are significantly better for those with vaginal lesions measuring less than 3 cm, FIGO staging of vaginal melanomas does not accurately predict survival (Reid, 1989).

An effective treatment for vaginal melanoma has not yet been identified. Both wide local excision and radical surgery have been used, as well as radiotherapy and chemotherapy. Although melanomas generally are thought to be radioresistant, in one series, radiation therapy was found to provide local tumor control in women who had surgically unresectable disease (Miner, 2003).

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ENDOMETRIAL CANCER: INTRODUCTION

In the United States, endometrial cancer is the most common gynecologic malignancy. Worldwide each year, 142,000 women are diagnosed, and 42,000 women die from this disease (Amant, 2005). Risk factors include obesity and advancing age. As both of these become more prevalent, the incidence of endometrial cancer likely will similarly increase. Fortunately, patients typically seek medical attention early due to vaginal bleeding, and endometrial biopsy leads quickly to diagnosis. The primary treatment is hysterectomy with bilateral salpingo-oophorectomy (BSO) and lymphadenectomy for most women. Three quarters of patients will have stage I disease that is curable by surgery alone. Patients with more advanced disease typically require postoperative combination chemotherapy, radiotherapy, or both.

EPIDEMIOLOGY AND RISK FACTORS

One in 38 American women (2.6 percent) will develop endometrial cancer during their lifetime. In the United States, 39,080 new cases are estimated to develop in 2007, but only 7,400 deaths are expected. Most patients are diagnosed early and are cured subsequently. As a result, endometrial cancer is the fourth leading cancer in incidence but only the eighth leading cause of cancer deaths among women (Jemal, 2007). The average age at diagnosis is the early 60s (Creasman, 1998; Farley, 2000; Madison, 2004).

Numerous risk factors for developing endometrial cancer have been described (Table 33-1). In general, most risk factors are associated with direct or indirect creation of an excessive estrogen environment.

Table 33-1 Risk Factors for Endometrial Cancer

Factors Influencing Risk	Estimated Relative Risk[a]
Obesity	2â€“5
Polycystic ovarian syndrome	>5
Long-term use of high-dose menopausal estrogens	10â€“20
Early age of menarche	1.5â€“2
Late age of natural menopause	2â€“3
History of infertility	2â€“3
Nulliparity	3
Menstrual irregularities	1.5
Residency in North America or northern Europe	3â€“18
Higher level of education or income	1.5â€“2
White race	2

Older age	2â€"3
High cumulative doses of tamoxifen	3â€"7
History of diabetes, hypertension, or gallbladder disease	1.3â€"3
Long-term use of high-dose combination oral contraceptives	0.3â€"0.5
Cigarette smoking	0.5

[a] Relative risks depend on the study and referent group employed.

From Brinton, 2004, with permission.

Of these, *obesity* is the most common cause of endogenous overproduction of estrogen. Excessive adipose tissue increases peripheral aromatization of androstenedione to estrone. In premenopausal women, elevated estrone levels trigger abnormal feedback in the hypothalamic-pituitary-ovarian axis. The clinical result is oligo- or anovulation. In the absence of ovulation, the endometrium is exposed to virtually continuous estrogen stimulation without subsequent progestational effect and menstrual withdrawal bleeding.

Unopposed estrogen therapy is the next most important potential inciting factor. Fortunately, the malignant potential of continuous or sequentially administered estrogen was recognized more than three decades ago (Smith, 1975). Currently, it is rare to encounter a woman with a uterus who has been on unopposed estrogen for years. Instead, combined estrogen plus progestin hormonal therapy is prescribed routinely for postmenopausal women with a uterus to reduce their risk of endometrial cancer (Strom, 2006). There remain questions about how effective this combination strategy is at preventing endometrial cancer, but certainly it is superior to unopposed estrogen (Lacey, 2005).

Menstrual and reproductive factors are commonly associated with endometrial cancer whenever anovulation is present or the duration of uninterrupted menstrual cycles is prolonged. For example, early age of menarche and late age of menopause are both associated with increased risk (Wernli, 2006). Classically, women with polycystic ovarian syndrome are anovulatory and thus have an increased risk of developing endometrial cancer (Pillay, 2006).

Environment may predispose to endometrial cancer in several ways. Women in Western and developed societies have a much higher incidence (Parkin, 2005). Obvious confounding variables within these populations, such as obesity and low parity, account for much of this effect. However, a possible etiologic role for nutritionâ€"especially a high dietary content of animal fatâ€"is another explanation (Goodman, 1997). Immigrant populations tend to assume the risks of native populations within one or two generations, highlighting the importance of environmental factors (Liao, 2003).

Older age is another risk factor for developing endometrial cancer, with a peak incidence among women in their 70s. Overall, about 80 percent of diagnoses occur in postmenopausal women older than 55 years (Schottenfeld, 1995). Fewer than 5 percent of endometrial cancers develop in patients younger than 40 years.

Family history is also linked to endometrial cancer. This cancer is the most common extracolonic manifestation in hereditary nonpolyposis colorectal cancer (HNPCC), also known as *Lynch syndrome* (Hemminki, 2005). This autosomal dominant syndrome results primarily from germline mutations in the mismatch repair genes *MLH1* and *MSH2* . Mutation carriers have a risk of developing endometrial cancer that ranges from 40 to 60 percent. Among women, the endometrial cancer risk actually exceeds that for colorectal cancer (Aarnio, 1999; Dunlop, 1997). However, fewer than 5 percent of endometrial cancers are attributable to HNPCC (Hampel, 2006). In general, most familial cases develop in premenopausal women (Gruber, 1996).

BRCA1 and *BRCA2* mutation carriers also have a slightly elevated risk, but only because of frequent tamoxifen treatment of previous breast cancers (Beiner, 2007). In general, these mutations mainly predispose women to breast and ovarian cancerâ€"not endometrial cancer.

Tamoxifen is used in the treatment of breast cancer (see Chap. 12, Hormonal Therapy and Targeted Therapies). It causes a two- to

threefold higher risk of developing endometrial cancer by having a modest "unopposed" estrogenic effect on the endometrium. The level of risk also increases linearly with the duration of therapy and the cumulative dose (van Leeuwen, 1994).

Most data suggest that endometrial cancers that develop in patients receiving tamoxifen exhibit the same stage, grade, and prognosis distribution as those in nonusers (Fisher, 1994). The increased risk of endometrial cancer occurs almost exclusively in postmenopausal women (Fisher, 1998). Premenopausal women treated with tamoxifen have no known increased risk of uterine cancer and do not require any additional monitoring beyond routine gynecologic care (American College of Obstetricians and Gynecologists, 2006).

Coexisting medical conditions such as diabetes mellitus, hypertension, and gallbladder disease are commonly associated with endometrial cancer (Morimoto, 2006; Soliman, 2005). In general, these are frequent sequelae of obesity and an environment of chronic excess estrogen.

Oral contraceptive use for a period of at least one year confers as much as a 30- to 50-percent reduced risk of endometrial cancer, and risk reduction extends for 10 to 20 years (Stanford, 1993). In essence, the progestin component has a chemopreventive biologic effect on the endometrium. The potency of the progestin in most oral contraceptives is adequate, but higher progestin potency may be more protective among obese women (Maxwell, 2006). Progesterone intrauterine devices (IUDs) also confer long-term protection against endometrial cancer (Tao, 2006).

Smokers have a lower risk of developing endometrial cancer. The biologic mechanism is multifactorial but in part involves reduced levels of circulating estrogens through weight reduction, an earlier age at menopause, and altered hormonal metabolism. Both current smoking and past smoking have a long-lasting influence (Viswanathan, 2005).

ENDOMETRIAL HYPERPLASIA

Most endometrial cancers arise following progression of histologically distinguishable hyperplastic lesions. In fact, endometrial hyperplasia is the only known direct precursor of invasive disease. The major criterion for establishing the diagnosis of hyperplasia is thickening of the endometrium due to an increase in the number and size of irregularly proliferating glands (Kurman, 1994). In the absence of thickening, lesions are best designated as *disordered proliferative endometrium* or *focal glandular crowding.* Endometrial hyperplasia represents a continuum of histopathologic findings that are difficult to differentiate by standard characteristics. These lesions range from anovulatory endometrium to monoclonal precancers.

Classification

WORLD HEALTH ORGANIZATION

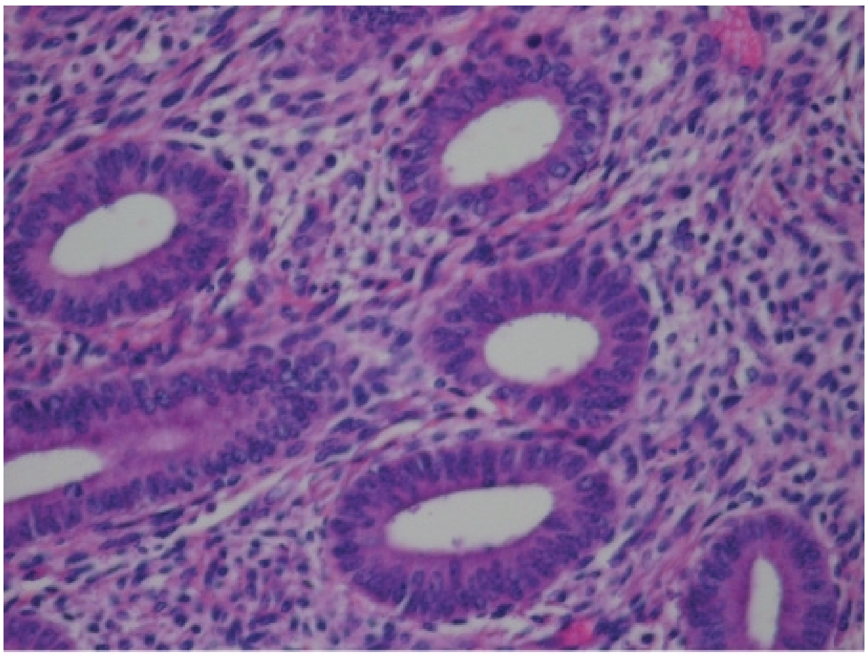
The classification system used by the World Health Organization (WHO) and the International Society of Gynecological Pathologists designates four different types with varying malignant potential (Table 33-2) (Kurman, 1985). Hyperplasias are classified as *simple* or *complex* based on the absence or presence of architectural abnormalities such as glandular complexity and crowding (Figs. 33-1 and 33-2). Most important, hyperplasias are further designated as *atypical* if they demonstrate cytologic (i.e., nuclear) atypia. Only atypical endometrial hyperplasias are clearly associated with the subsequent development of adenocarcinoma. Simple atypical hyperplasia is a relatively uncommon diagnosis. In general, most atypical hyperplasias have a complex architecture (Figs. 33-3 and 33-4).

Table 33-2 World Health Organization Classification of Endometrial Hyperplasia

Types	Progressing to Cancer(%)
Simple hyperplasia	1
Complex hyperplasia	3
Simple atypical hyperplasia	8
Complex atypical hyperplasia	29

From Kurman, 1985, with permission.

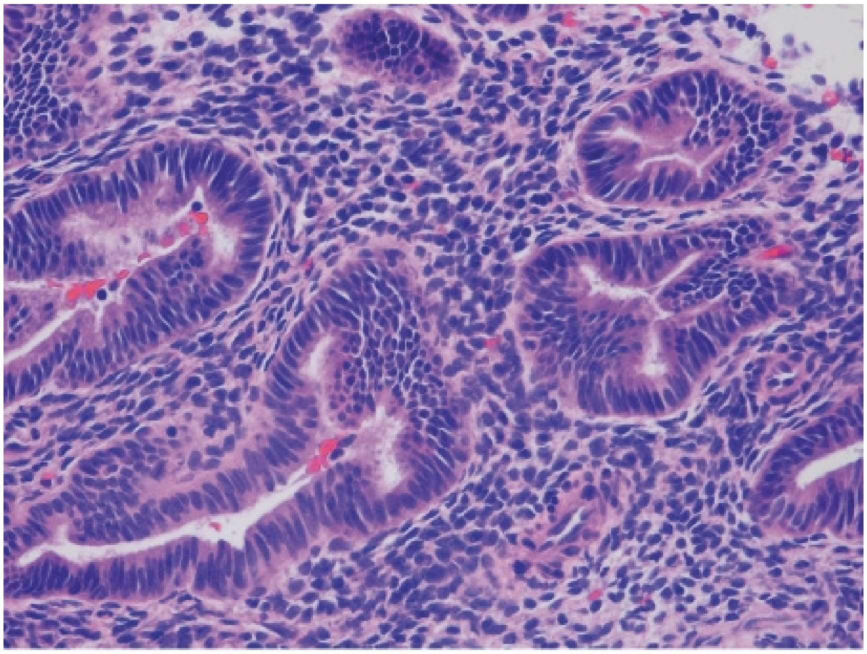
FIGURE 33-1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Simple hyperplasia without atypia shows glandular crowding and mild architectural complexity. *(Courtesy of Dr. Raheela Ashfaq.)*

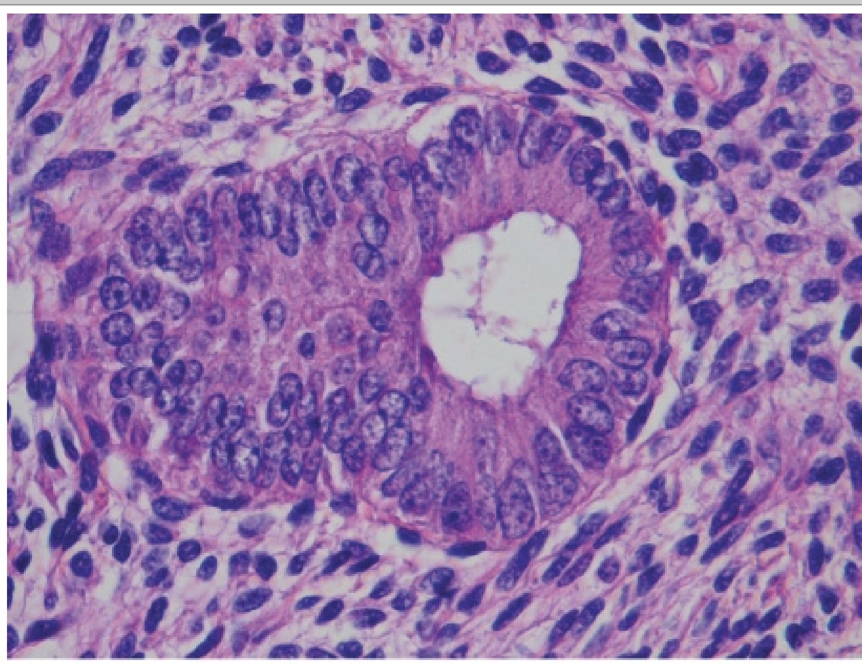
FIGURE 33-2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

In contrast, complex hyperpasia without atypia shows pronounced glandular complexity. *(Courtesy of Dr. Raheela Ashfaq.)*

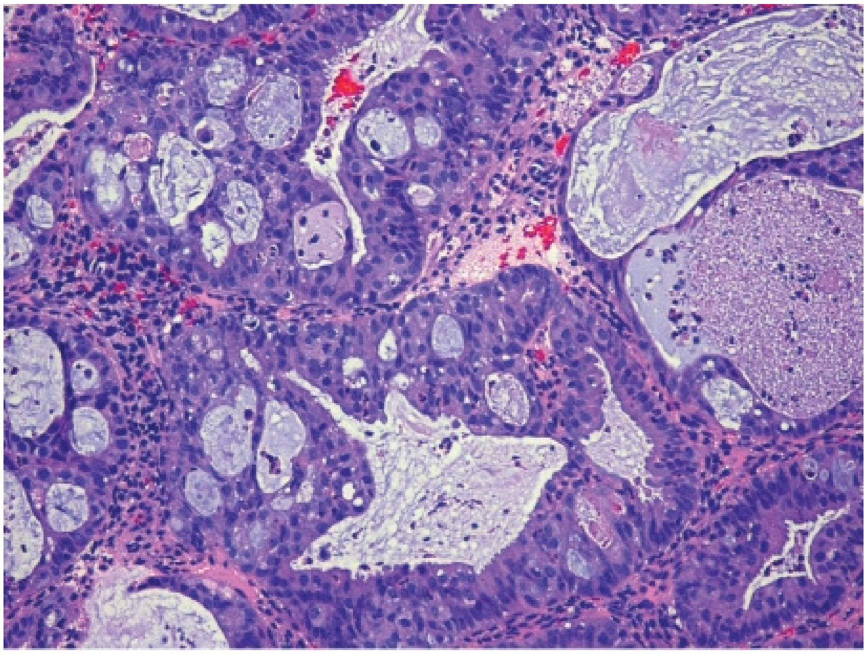
FIGURE 33-3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Simple atypical hyperplasia. Atypia in simple or complex hyperplasia refers to nuclear atypicality. This is evidenced by nuclear enlargement, nucleoli, variation in nuclear size and shape, and atypical mitoses. *(Courtesy of Dr. Raheela Ashfaq.)*

FIGURE 33-4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Complex atypical hyperplasia. *(Courtesy of Dr. Raheela Ashfaq.)*

Although endometrial hyperplasias are formally classified into these four different groups, they tend to be morphologically heterogeneous both within and between individual patients. This histologic diversity explains why only a small number of conserved features are useful as diagnostic criteria. As a result, reproducible scoring of cytologic atypia is often challenging, particularly with a small amount of tissue from a biopsy sample.

ENDOMETRIAL INTRAEPITHELIAL NEOPLASIA

Recently, the term *endometrial intraepithelial neoplasia* (EIN) has been introduced to more accurately distinguish the two very different clinical categories of hyperplasia: (1) normal polyclonal endometria diffusely responding to an abnormal hormonal environment, and (2) intrinsically proliferative monoclonal lesions that arise focally and confer an elevated risk of adenocarcinoma (Mutter, 2000). This nomenclature emphasizes the malignant potential of endometrial precancers, in keeping with similar precedents in the cervix, vagina, and vulva.

Using this system, nonatypical anovulatory or prolonged estrogen-exposed endometria generally are designated as *endometrial hyperplasias.* In contrast, *endometrial intraepithelial neoplasia* is used to describe all endometria delineated as premalignant by a combination of three morphometric features. These features reflect glandular volume, architectural complexity, and cytologic abnormality. The EIN classification system is a more accurate and reproducible way of predicting progression to cancer but has not been implemented universally (Baak, 2005; Hecht, 2005).

Clinical Features

The risk factors for developing endometrial hyperplasia generally mirror those for invasive carcinoma (Anastasiadis, 2000; Ricci, 2002). Two thirds of women present with postmenopausal bleeding (Horn, 2004). However, almost any type of abnormal uterine

bleeding should prompt diagnostic evaluation (see Chap 8, Diagnosis).

Transvaginal sonography of endometrial thickness is a feasible method for predicting endometrial hyperplasia. In postmenopausal women with endometrial measurements of 5 mm or less, sonographic pathologic studies have demonstrated that bleeding can be attributed to endometrial atrophy (see Chap. 2, Endometrium). Those with a thicker endometrium warrant biopsy. Alternatively, Pipelle (CooperSurgical, Trumbull, CT) office biopsy or outpatient dilatation and curettage (D&C) may be selected initially (Merisio, 2005). Grossly, hyperplastic endometrium is not distinctive, and thus direct visual identification using hysteroscopy is inaccurate (Garuti, 2005).

Occasionally, an adnexal mass may be palpable on examination. Although this most likely is a benign ovarian cyst, any solid features noted during transvaginal sonography should raise the possibility of a coexisting ovarian granulosa cell tumor. These tumors produce an excessive estrogenic environment that results in up to a 30-percent risk of endometrial hyperplasia or, less commonly, carcinoma (see Chap. 36, Granulosa Cell Tumors) (Ayhan, 1994).

Treatment

Management of women with endometrial hyperplasia depends mainly on the patient's age and the presence or absence of cytologic atypia. However, nonsurgical therapy is inherently risky due to the inconsistency of diagnosis and uncertainty in predicting the natural history of individual lesions. In addition, there is no way to anticipate which types will involute with progestin therapy. However, as long as an endometrial sample is representative and a provider has no reason to suspect a coexisting invasive carcinoma, the decision to treat endometrial hyperplasia through hormonal or surgical means relies on clinical judgment.

NONATYPICAL ENDOMETRIAL HYPERPLASIA

Premenopausal Women

Premenopausal women with nonatypical endometrial hyperplasia typically require a 3- to 6-month course of low-dose progestin therapy. Cyclic medroxyprogesterone acetate (MPA) (Provera, Pfizer, New York, NY) given orally for 12 to 14 days each month at a dose of 10 to 20 mg daily is commonly used. Another frequently used option is to initiate a combination oral contraceptive pill. Progesterone-containing IUDs are also effective (Wildemeersch, 2003). In some patients, hysteroscopic endometrial ablation can be curative, but posttreatment surveillance is more difficult, and subsequent hysterectomy rates are high (Jarvela, 2005). Although lesions may regress spontaneously without therapy, progestins generally are used to address the underlying etiology, i.e., chronic anovulation and excess estrogen (Terakawa, 1997). If no residual hyperplastic endometrium is found during surveillance biopsy, then patients should be continued on progestins and be monitored until menopause. An additional endometrial biopsy is required for new bleeding.

In general, biopsies should be avoided when a patient is taking progestins because this hormone confounds the pathologic diagnosis through modification of endometrial morphology. Endometrial shedding during a withdrawal bleed is also an integral component of medication-induced ablation and should be completed before assessing persistence. Waiting 2 to 6 weeks after hormone withdrawal before biopsy solves these problems.

Postmenopausal Women

Postmenopausal women with nonatypical endometrial hyperplasia also may be treated with low-dose cyclic MPA or a continuous 2.5 mg/day regimen. However, it is particularly important in older women to be confident that an adequate sample has been obtained to exclude cytologic atypia. A D&C may be indicated in some circumstances. For instance, occasionally, tissue volume with Pipelle sampling is scant, or bleeding symptoms are more prominent than expected.

In practice, postmenopausal patients with simple hyperplasia often are followed without therapy. Complex hyperplasia without atypia usually is treated with progestins. Office endometrial biopsy is performed annually to surveil these women.

Response of Nonatypical Endometrial Hyperplasia to Progestins

The overall clinical and pathologic regression rates of progestin therapy exceed 90 percent for nonatypical endometrial hyperplasia (Rattanachaiyanont, 2005). Patients with persistent disease on repeated biopsy should be switched to a higher-dose regimen such as MPA 40 to 100 mg orally daily or megestrol acetate (Megace, Bristol-Myers Squibb, New York, NY), 160 mg daily. Again, the

clinician must confirm that hormonal ablation has occurred by resampling the endometrium after a suitable therapeutic interval. Hysterectomy also should be reconsidered for lesions that are refractory to medical management.

ATYPICAL ENDOMETRIAL HYPERPLASIA

Hysterectomy is the best treatment for women at any age with atypical endometrial hyperplasia because the risk of concurrent subclinical invasive disease is high (Horn, 2004). Premenopausal women who strongly wish to preserve fertility are the main exception. High-dose progestin therapy may be most appropriate for highly motivated patients (Randall, 1997). Poor surgical candidates also may warrant an attempt at hormonal ablation with progestins. Resolution of the hyperplasia must be confirmed by serial endometrial biopsies every 3 months until response is documented. Otherwise, hysterectomy should be recommended (Orr, 2005). Following hyperplasia resolution, surveillance should continue long term due to the potential for eventual progression to carcinoma (Rubatt, 2005).

The Gynecologic Oncology Group (GOG) performed a prospective cohort study of 289 patients who had a diagnosis of atypical endometrial hyperplasia in the community. Participants underwent hysterectomy within 3 months of their biopsy, and 43 percent were found to have a concurrent endometrial carcinoma (Trimble, 2006). Results demonstrate the futility of trying to make an accurate diagnosis before hysterectomy and the potential risks of conservative hormonal treatment.

Generalists in obstetrics and gynecology who perform hysterectomy for atypical endometrial hyperplasia should be especially wary of the possibility of invasive disease and the need for surgical staging. If a gynecologic oncologist is not available, then some reports have suggested that hysteroscopic visualization may be able to identify a coexisting infiltrating carcinoma and thereby aid appropriate referral (Garuti, 2006). At a minimum, peritoneal washings should be obtained prior to performing a hysterectomy. In addition, the uterus should be opened and examined in the operating room. Any suspicion for invasive disease is an appropriate indication for intraoperative consultation with a gynecologic oncologist.

ENDOMETRIAL CANCER

Pathogenesis

Endometrial cancer is a biologically and histologically diverse group of neoplasms characterized by a dualistic model of pathogenesis. Type I endometrioid adenocarcinomas comprise 75 percent of all cases. They are estrogen dependent, low grade, and derived from atypical endometrial hyperplasia. In contrast, type II cancers usually have serous or clear cell histology, no precursor lesion, and a more aggressive clinical course (Table 33-3). The morphologic and clinical differences are paralleled by genetic distinctions in that type I and II tumors carry mutations of independent sets of genes (Hecht, 2006).

Table 33-3 Type I and II Endometrial Carcinoma: Distinguishing Features

Feature	Type I	Type II
Unopposed estrogen	Present	Absent
Menopausal status	Pre- and perimenopausal	Postmenopausal
Hyperplasia	Present	Absent
Race	White	Black
Grade	Low	High
Myometrial invasion	Minimal	Deep
Specific subtypes	Endometrioid	Serous, clear cell
Behavior	Stable	Aggressive

From Kurman, 1994, with permission.

The two pathways of endometrial cancer pathogenesis obviously have significant overlap and result in a spectrum of histologic features. However, this dualistic view has therapeutic ramifications for novel treatment strategies that target high-risk disease (Cerezo, 2006).

Prevention

SCREENING

There is currently no role for routine screening of endometrial cancer for women at average or increased risk (see Table 33-1). Instead, at the onset of menopause, women should be informed about the risks and symptoms of endometrial cancer. They should be strongly encouraged to report any unexpected bleeding or spotting to their health care provider (American College of Obstetricians and Gynecologist, 2006; Smith, 2003).

However, annual screening by endometrial sampling should begin at age 35 years in women at high risk for endometrial cancer due to HNPCC (Burke, 1997; Smith, 2003). Potential mutation carriers of this syndrome may be identified if they have first- or second-degree family members diagnosed with more than one endometrial, colon, or ovarian cancer. Referral for genetic counseling can further clarify the risk to predict which patients may benefit from specific germline testing (Balmana, 2006; Chen, 2006). Since endometrial cancer is the most common "sentinel cancer," obstetrician-gynecologists play a pivotal role in identification of women with HNPCC (Lu, 2005).

PROPHYLACTIC SURGERY

Since women with the HNPCC have such a high lifetime risk of developing endometrial cancer (40 to 60 percent), prophylactic hysterectomy is another option. In a cohort of 315 HNPCC mutation carriers, Schmeler and associates (2006) confirmed the benefit of this approach by reporting a 100-percent risk reduction. In general, BSO also should be performed because of the 10- to 12-percent lifetime risk of ovarian cancer in these women.

Diagnosis

SIGNS AND SYMPTOMS

Early diagnosis of endometrial cancer is almost entirely dependent on the prompt recognition and evaluation of irregular vaginal bleeding. In premenopausal women, a clinician must maintain a high index of suspicion for a history of prolonged, heavy menstruation or intermenstrual spotting because many other benign disorders give rise to similar symptoms (see Chap. 8, Incidence). Postmenopausal bleeding is particularly worrisome, leading to a 5- to 10-percent likelihood of diagnosing endometrial carcinoma (Gredmark, 1995; Iatrakis, 1997). Abnormal vaginal discharge may be another symptom in older women.

Unfortunately, some patients do not seek medical attention despite months or years of heavy, irregular bleeding. In more advanced disease, pelvic pressure and pain may reflect uterine enlargement or extrauterine tumor spread. Patients with serous or clear cell tumors often present with signs and symptoms suggestive of advanced epithelial ovarian cancer (see Chap. 35, Epithelial Ovarian Cancer).

PAPANICOLAOU TEST

Historically, the Pap smear has not been a sensitive tool to diagnose endometrial cancer, and 50 percent of women with endometrial cancer will have normal findings (Gu, 2001). Liquid-based cytology appears to increase the detection of glandular abnormalities but not enough to change clinical practice (Guidos, 2000; Schorge, 2002).

Benign endometrial cells are recorded occasionally on a routine Pap smear in women 40 years and older. In premenopausal women, this is often a finding of limited importance, especially if the smear is obtained following menses. However, postmenopausal women with such findings have nearly a 3- to 5-percent risk of endometrial cancer (Simsir, 2005). In those using hormone-replacement therapy, the prevalence of benign endometrial cells on smears is increased, and the risk of malignancy is less (1 to 2 percent) (Mount, 2002). Although endometrial biopsy should be considered in asymptomatic postmenopausal women if this finding is reported, most patients ultimately diagnosed with hyperplasia or cancer have concomitant abnormal bleeding

(Ashfaq, 2001).

ENDOMETRIAL SAMPLING

Office Pipelle biopsy is always preferred for the initial evaluation of women with bleeding suspicious for malignancy (Feldman, 1993). However, if sampling techniques fail to provide sufficient diagnostic information, or if abnormal bleeding persists, D&C may be required to clarify the diagnosis (Gordon, 1999).

Outpatient hysteroscopy has proved less helpful in diagnosing hyperplasia (Ben Yehuda, 1998). Moreover, diagnostic hysteroscopy has been associated with an increased incidence of positive peritoneal cytology during subsequent staging surgery (Obermair, 2000; Zerbe, 2000). Although this may not worsen an individual patient's prognosis, it does increase the initial cancer stage. As a result, physicians should be wary about performing fluid hysteroscopy routinely if a malignancy is suspected.

LABORATORY TESTING

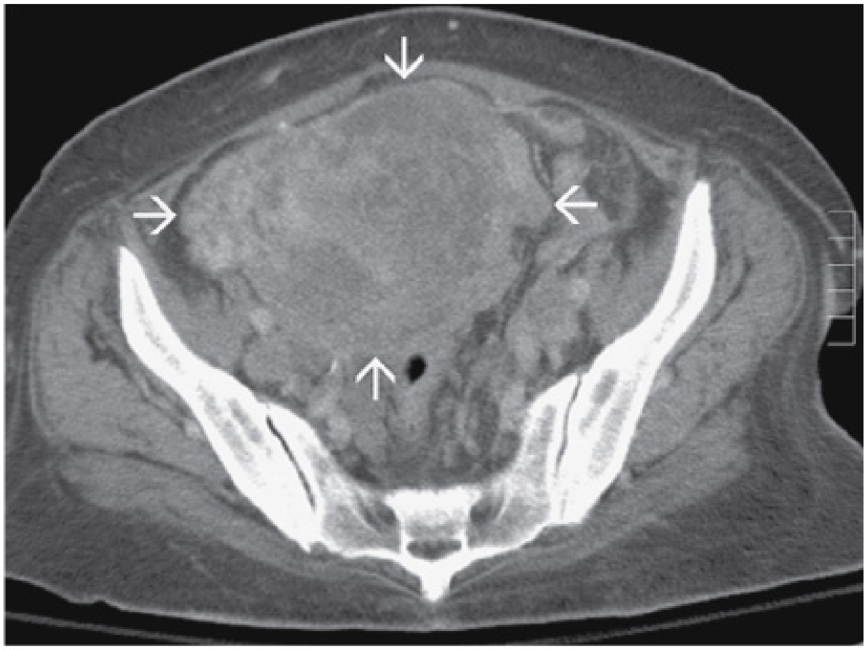
The only clinically useful tumor marker in the management of endometrial cancer is measurement of a serum CA125 level. Preoperatively, an elevated titer indicates the possibility of more advanced disease (Powell, 2005). In practice, it is most useful in patients with advanced disease or serous subtypes to assist in monitoring response to therapy or during posttreatment surveillance. However, even in this setting, it has limited utility in the absence of other clinical findings (Price, 1998).

IMAGING STUDIES

In general, for women with a well-differentiated type I endometrioid tumor, chest radiograph is the only required preoperative imaging study. All other preoperative testing is directed toward general surgical preparation.

Computed tomographic (CT) scanning or magnetic resonance (MR) imaging usually is not necessary (Orr, 2005). However, MR imaging occasionally can help to distinguish an endometrial cancer with cervical extension from a primary endocervical adenocarcinoma (Nagar, 2006). Moreover, women with serous features or other high-risk histology on preoperative biopsy and those with physical examination findings suggesting advanced disease are most appropriate for abdominal pelvic CT scanning (Fig. 33-5). In these cases, advance knowledge of intra-abdominal disease may be helpful in guiding treatment.

FIGURE 33-5



A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

CT images in the axial plane (**A** , **B**) of a 61-year-old woman with endometrial cancer. **A.** Massively enlarged and inhomogeneous uterus **(arrows)** in the upper pelvis. **B.** At the level of the aortic bifurcation, bilateral lymph nodes are seen **(arrows)** consistent with lymph node involvement. (Courtesy of Dr. Diane Twickler.)

Role of the Generalist

Although most endometrial cancers are cured by hysterectomy and BSO, primary management by gynecologic oncologists results in an efficient use of health care resources and minimizes potential morbidity (MacDonald, 2005; Roland, 2004). Therefore, preoperative consultation generally is advisable for any patient with endometrial cancer who is being prepared for surgery by a generalist in obstetrics and gynecology. Young or perimenopausal women with grade 1 endometrioid adenocarcinoma in a background of atypical endometrial hyperplasia are possible exceptions. However, the old axiom of a nodal dissection not being required for a grade 1 tumor no longer applies because many women will have more advanced disease than predicted by preoperative prognostic factors. In addition, intraoperative evaluation of depth of invasion is less accurate than previously thought (Frumovitz, 2004a).

Postoperatively, a gynecologic oncologist should be consulted whenever there is evidence for cervical extension, extrauterine disease, or positive peritoneal washings. In many cases, early-stage patients treated by surgery alone will return to their primary obstetrician-gynecologist for surveillance. Consultation again is recommended if recurrent disease is diagnosed or suspected.

When an endometrial cancer is diagnosed unexpectedly after hysterectomy performed by a generalist for other indications, consultation is also recommended. Possible therapeutic options include no further therapy and surveillance only, reoperation to complete surgical staging, or radiotherapy to prevent local recurrence. In general, the survival advantages of staging must be weighed against the complications from another surgical procedure (Orr, 2005). Fortunately, the advent of laparoscopic restaging has resulted in the potential for less morbidity in selected patients (Spirtos, 2005).

Pathology

There is a broad spectrum of aggressiveness within the histopathologic types of endometrial cancer (Table 33-4). Most patients have endometrioid adenocarcinomas that behave indolently. However, some will have an unfavorable histology that portends a much more aggressive tumor. In addition, the degree of tumor differentiation is an important predictor of disease spread. Tumors that arise following pelvic radiation differ from sporadic endometrial cancers by having a preponderance of high-stage, high-grade, and high-risk histologic subtypes (Pothuri, 2003). Effectively managing women with endometrial cancer requires an understanding of these interrelated clinical features.

Table 33-4 World Health Organization Histologic Classification of Endometrial Carcinoma
Endometrioid adenocarcinoma
Variant with squamous differentiation
Villoglandular variant
Secretory variant
Ciliated cell variant
Mucinous carcinoma
Serous carcinoma
Clear cell carcinoma
Squamous cell carcinoma
Mixed cell carcinoma

Undifferentiated carcinoma

From Silverberg, 2003, with permission.

HISTOLOGIC GRADE

The most widely used grading system for endometrial carcinoma is the three-tiered International Federation of Gynecology and Obstetrics (FIGO) system (Table 33-5). Grade 1 lesions typically have a good prognosis. Grade 2 tumors have an intermediate prognosis. Grade 3 cancers frequently have a poor prognosis and are associated with an increased potential for myometrial invasion and nodal metastasis.

Table 33-5 Histopathologic Criteria for Assessing Grade

Grade	Definition
1	≦5% of a nonsquamous or nonmorular solid growth pattern
2	6â€"50% of a nonsquamous or nonmorular solid growth pattern
3	> 50% of a nonsquamous or nonmorular solid growth pattern

From Pecorelli, 1999, with permission.

Histologic grading primarily should be determined microscopically by the tumor's architectural growth pattern (Zaino, 1994). However, there are a few exceptions, and the optimal method for determining grade is somewhat controversial. Nuclear atypia that is inappropriately advanced relative to the architectural grade raises a grade 1 or 2 tumor by one level. For example, a grade 2 lesion based on architectural features may be increased to a grade 3 lesion if significant nuclear atypia is present. This modification was shown to have prognostic utility in a GOG study of 715 endometrioid adenocarcinomas that were reviewed (protocol 33) (Zaino, 1995). Based on the FIGO system, nuclear grading also takes precedent for all serous and clear cell adenocarcinomas (Pecorelli, 1999).

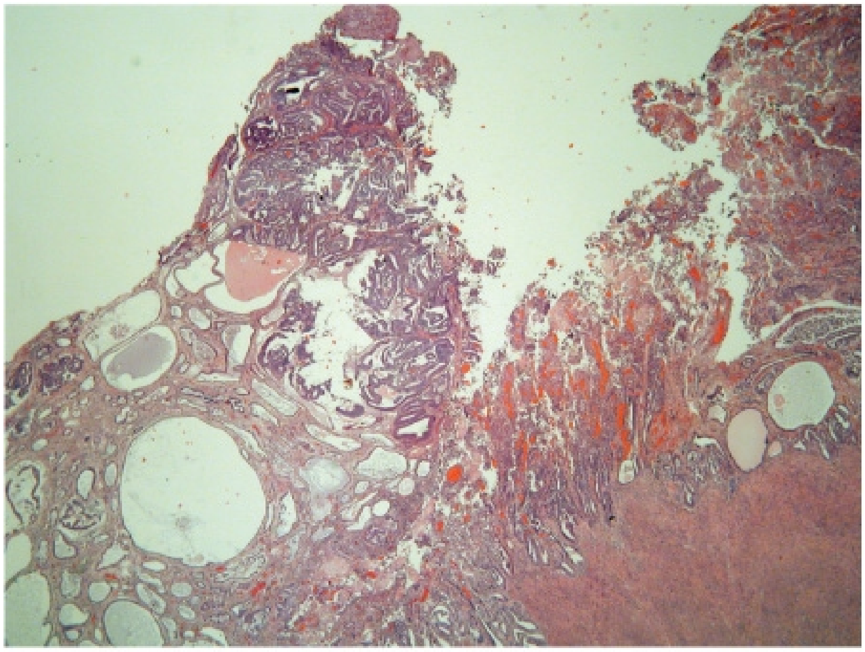
In an effort to improve the reproducibility and prognostic importance of the FIGO system, a binary architectural grading system has been proposed recently (Lax, 2000; Scholten, 2005). The simplicity of dividing tumors into low- and high-grade lesions based on the proportion of solid growth (≦50 percent or >50 percent, respectively) is attractive and appears to have value. This approach, however, has not been implemented widely in clinical practice.

HISTOLOGIC TYPE

Endometrioid Adenocarcinoma

The most common histologic type of endometrial cancer is endometrioid adenocarcinoma, accounting for more than 75 percent of cases. This tumor characteristically contains glands that resemble those of the normal endometrium (Fig. 33-6). The concomitant presence of hyperplastic endometrium typically correlates with a low-grade tumor and a lack of myometrial invasion. However, when the glandular component decreases and is replaced by solid nests and sheets of cells, the tumor is classified as a higher grade (Silverberg, 2003). In addition, an atrophic endometrium is associated more frequently with high-grade lesions that are commonly metastatic (Kurman, 1994).

FIGURE 33-6



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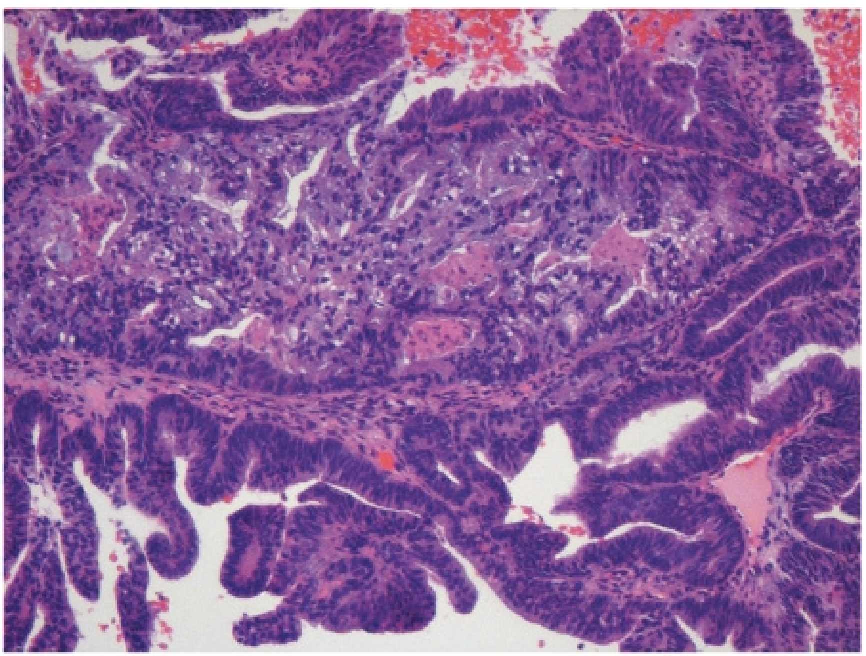
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



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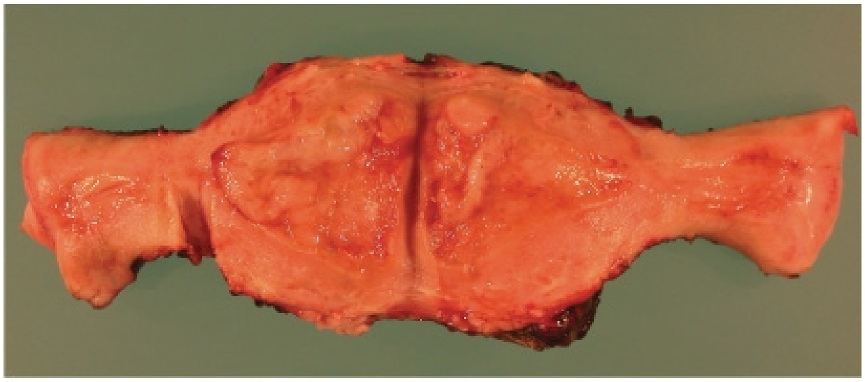

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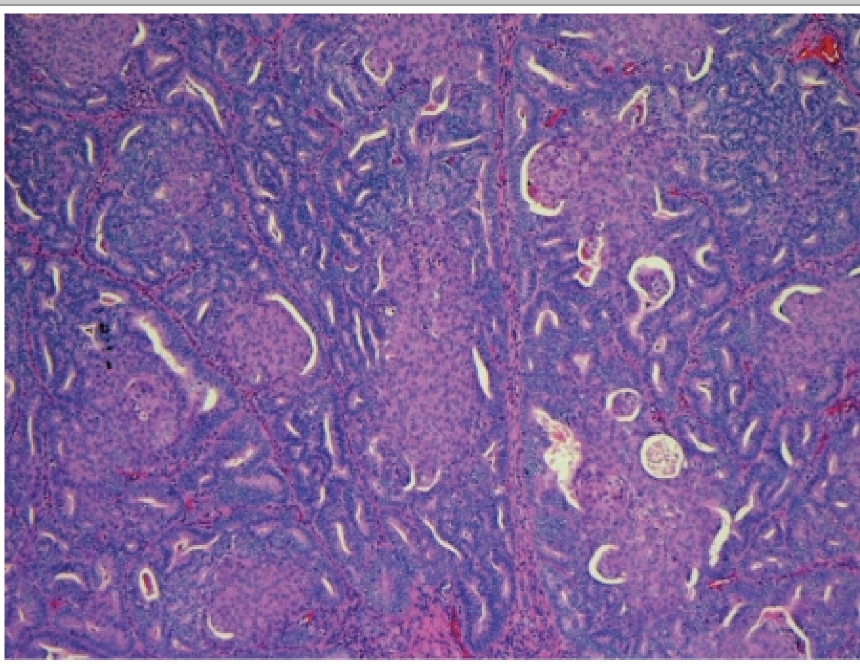
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Endometrioid adenocarcinoma. **A.** Low-power magnification of an endometrioid adenocarcinoma arising in a background of hyperplasia. **B.** High-power view of an endometrioid adenocarcinoma. **C.** Gross photomicrograph of a polypoid endometrioid adenocarcinoma. *(Courtesy of Dr. Raheela Ashfaq.)*

In addition to the characteristic appearance described, endometrioid adenocarcinomas may display variant forms (see Table 33-4). These include endometrioid adenocarcinoma with squamous differentiation and villoglandular, secretory, and ciliated cell variants (Figs. 33-7 and 33-8). In general, the biologic behavior of these variant tumors reflects that of classic endometrial adenocarcinoma.

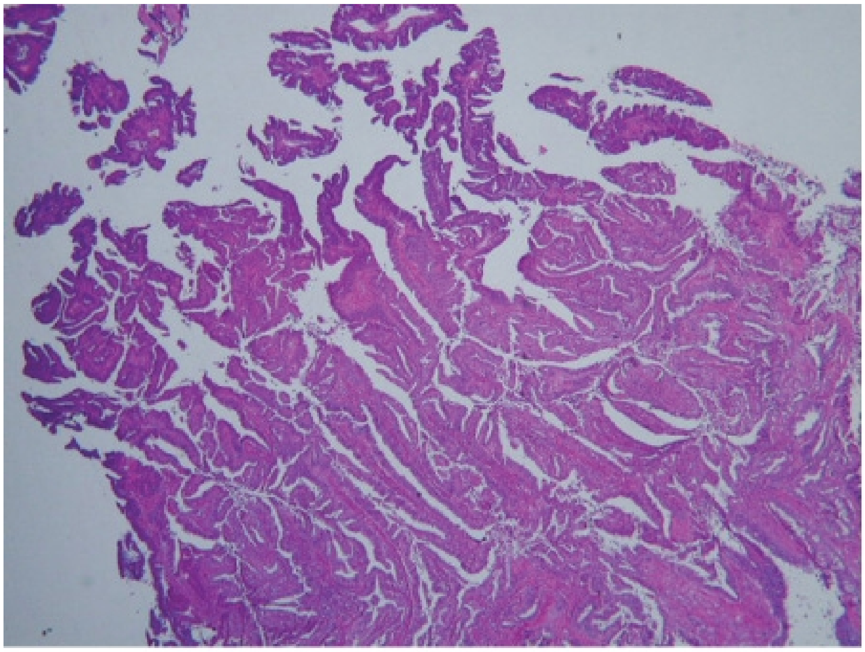
FIGURE 33-7



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Endometrioid adenocarcinoma with squamous differentiation. *(Courtesy of Dr. Raheela Ashfaq.)*

FIGURE 33-8



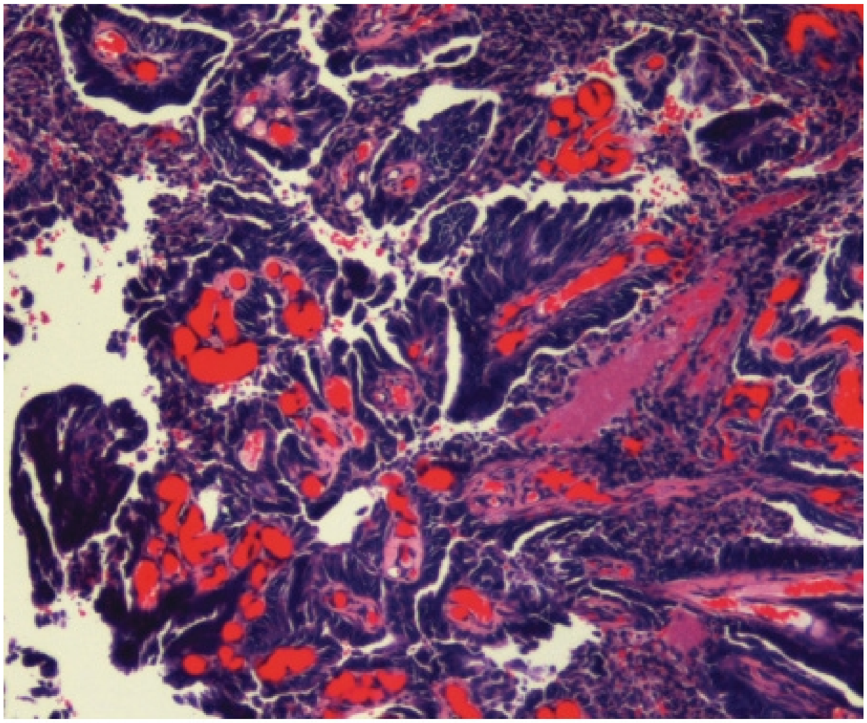
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Villoglandular endometrial adenocarcinomas are generally low grade and have a predominant papillary pattern with thin papillae and well-defined fibrovascular cores. *(Courtesy of Dr. Raheela Ashfaq.)*

Serous Carcinoma

Accounting for about 5 to 10 percent of endometrial cancers, serous carcinoma typifies the highly aggressive type II tumors that arise from the atrophic endometrium of older women (Jordan, 2001). There is typically a complex pattern of papillary growth with cells demonstrating marked nuclear atypia (Fig. 33-9). Commonly referred to as *uterine papillary serous carcinoma* (UPSC), its histologic appearance resembles epithelial ovarian cancer, and psammoma bodies are seen in 30 percent of patients (Fig. 33-10) (Silverberg, 2003).

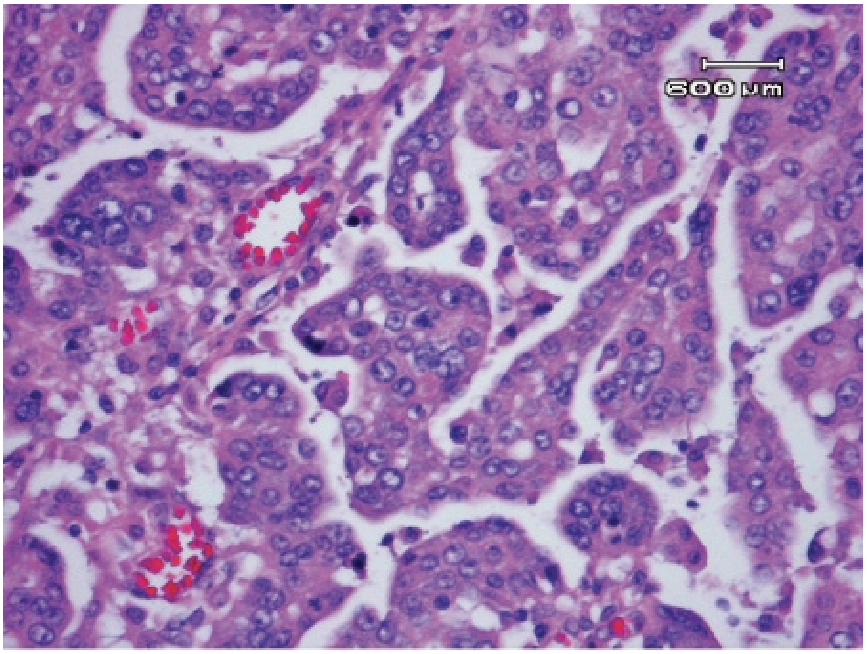
FIGURE 33-9



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Uterine papillary serous carcinoma (low magnification). Uterine papillary serous carcinomas are high-grade, aggressive tumors. These tumors are characterized by a complex papillary pattern. *(Courtesy of Dr. Raheela Ashfaq.)*

FIGURE 33-10

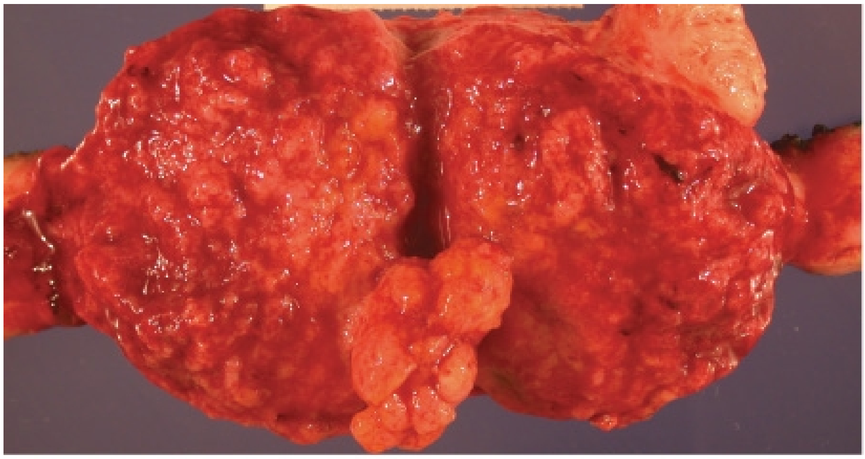


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Uterine papillary serous carcinoma (high magnificiation). Tumor cells are arranged in papillae and usually are pleomorphic with high mitotic activity *(Courtesy of Dr. Raheela Ashfaq.)*

Grossly, the tumor is exophytic with a papillary appearance emerging from a small, atrophic uterus (Fig. 33-11). These tumors occasionally may be confined within a polyp and have no evidence for spread (Carcangiu, 1992). However, UPSC has a known propensity for myometrial and lymphatic invasion. Intraperitoneal spread, such as omental caking, which is unusual for typical endometrioid adenocarcinoma, is also common even when myometrial invasion is minimal or absent (Fig. 33-12) (Sherman, 1992). As a result, it may be impossible to distinguish UPSC from epithelial ovarian cancer during surgery. Similar to ovarian carcinoma, these tumors usually secrete CA125, and serial serum measurements are a useful marker to monitor the disease postoperatively. Uterine papillary serous carcinoma is an aggressive cell type, and women with mixed endometrial cancers containing as little as 25 percent of UPSC have the same survival as those with pure serous carcinoma (Kurman, 1994).

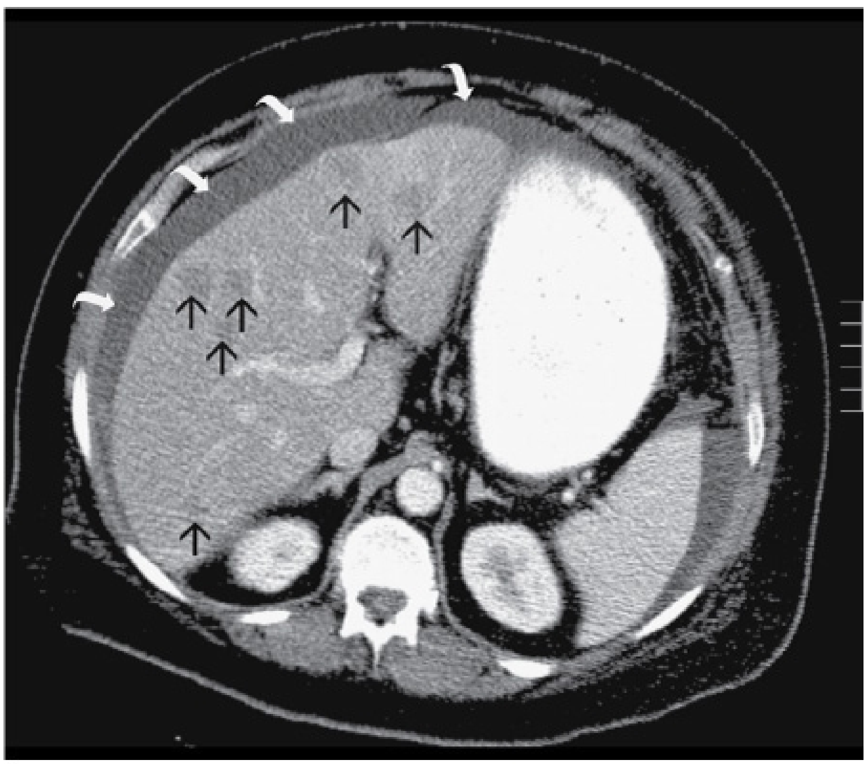
FIGURE 33-11



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Uterine papillary serous carcinoma (gross picture). *(Courtesy of Dr. Raheela Ashfaq.)*

FIGURE 33-12



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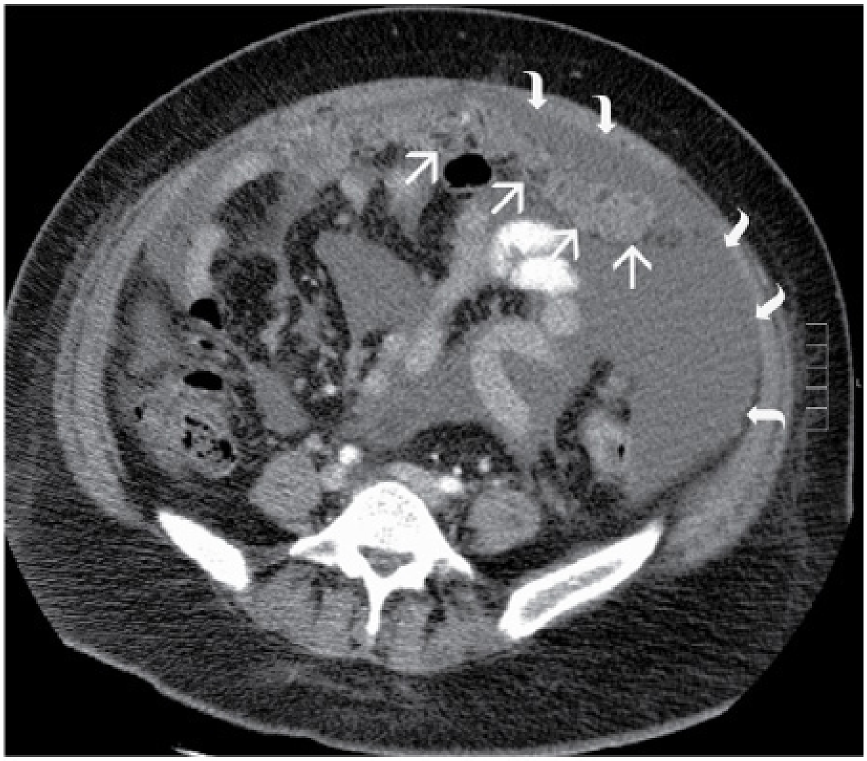

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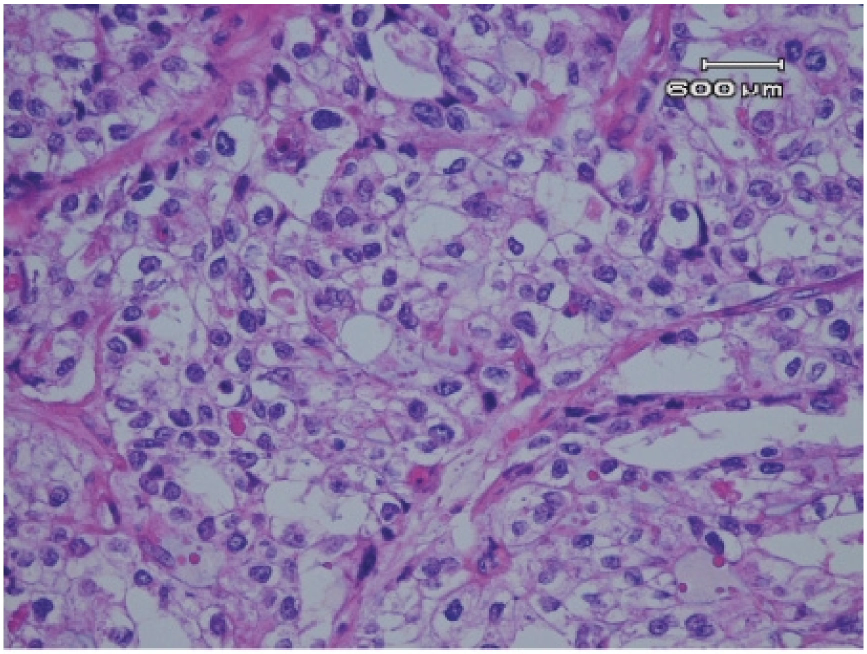
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

CT images of liver metastases, ascites, and omental caking in a 51-year-old woman with endometrial cancer. **A.** Black arrows demarcate the multiple low-density areas in the liver consistent with a metastatic process and ascites **(curved white arrows)** surrounding the liver. **B.** A more caudal image reveals omental caking **(white arrows)** surrounded by massive ascites **(curved white arrows)** . *(Courtesy of Dr. Diane Twickler.)*

Clear Cell Carcinoma

Fewer than 5 percent of endometrial cancers are clear cell variants, but this is the other major type II tumor (Abeler, 1991). The microscopic appearance may be predominantly solid, cystic, tubular, or papillary. Most frequently, it consists of a mixture of two or more of these patterns (Figs. 33-13 and 33-14) (Silverberg, 2003).

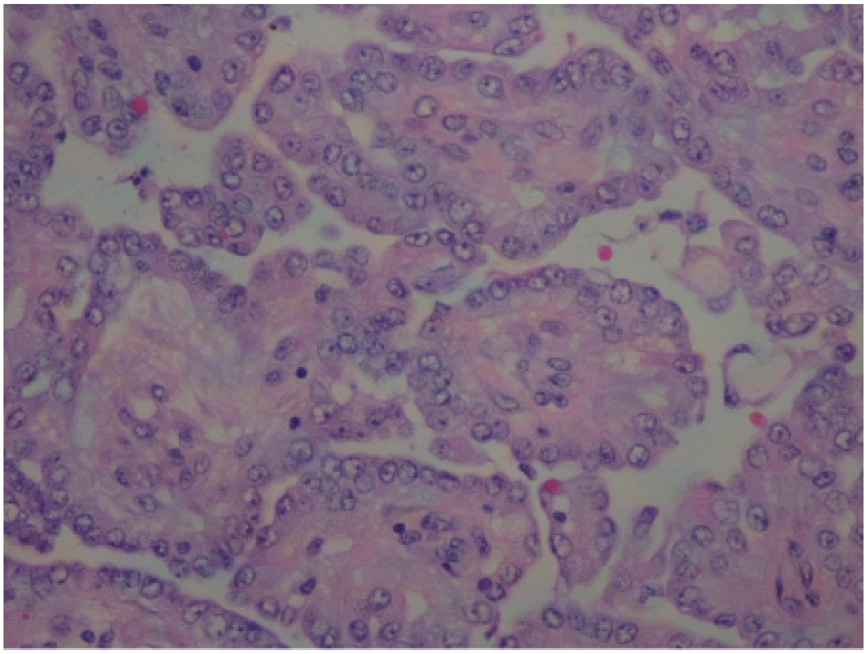
FIGURE 33-13



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Clear cell adenocarcinoma (solid type). Clear cell adenocarcinomas have abundant clear cytoplasm owing to high glycogen content and have varied growth patterns such as solid or papillary with oxyphilic and hobnail cells. *(Courtesy of Dr. Raheela Ashfaq.)*

FIGURE 33-14



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

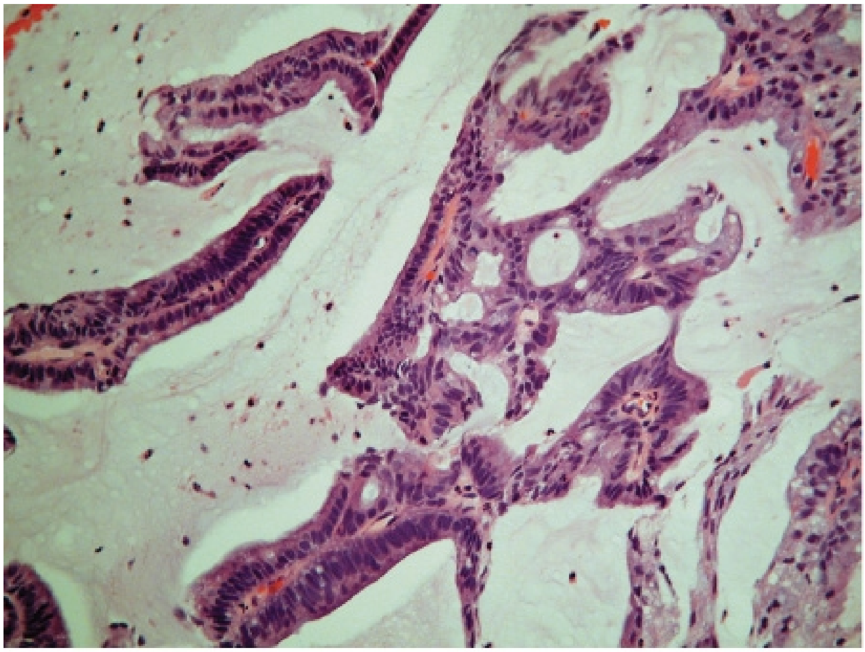
Clear cell carcinoma (papillary type). *(Courtesy of Dr. Raheela Ashfaq.)*

Endometrial clear cell adenocarcinomas are similar to those arising in the ovary, vagina, and cervix. Grossly, there are no characteristic features, but like UPSC, they tend to be high-grade, deeply invasive tumors. Patients often are diagnosed with advanced disease and have a poor prognosis (Hamilton, 2006).

Mucinous Carcinoma

About 1 to 2 percent of endometrial cancers have a mucinous appearance that comprises more than half the tumor. However, many endometrioid adenocarcinomas will have a focal component (Ross, 1983). Typically, mucinous tumors have a glandular pattern with uniform columnar cells and minimal stratification (Fig. 33-15). Almost all are stage I, grade 1 lesions with a good prognosis (Melhem, 1987). Since endocervical epithelium merges with the lower uterine segment, the main diagnostic dilemma is differentiating this tumor from a primary cervical adenocarcinoma. In this situation, immuno-staining may be helpful, but preoperative MR imaging may be required to further clarify the most likely site of origin.

FIGURE 33-15



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Mucinous carcinomas have endocervical-type mucin-producing cells. Note tumor cells floating in abundant mucin. *(Courtesy of Dr. Raheela Ashfaq.)*

Mixed Carcinoma

An endometrial cancer may demonstrate combinations of two or more pure types. To be classified as a mixed carcinoma, a component must comprise at least 10 percent of the tumor. Except for serous and clear cell histology, the combination of other types usually has no clinical significance. As a result, *mixed carcinoma* usually refers to an admixture of a type I (endometrioid adenocarcinoma and its variants) and type II carcinoma (Silverberg, 2003).

Undifferentiated Carcinoma

In 1 to 2 percent of endometrial cancers, there is no evidence of glandular, sarcomatous, or squamous differentiation. These undifferentiated tumors are characterized by proliferation of medium-sized, monotonous epithelial cells growing in solid sheets with no specific pattern. Overall, the prognosis is worse than in women with poorly differentiated endometrioid adenocarcinomas (Altrabulsi, 2005).

Rare Histologic Types

Fewer than 100 cases of *squamous cell carcinoma* of the endometrium have been reported. Diagnosis requires exclusion of an adenocarcinoma component and no connection with the squamous epithelium of the cervix (Varras, 2002). Typically, the prognosis is poor (Goodman, 1996). *Transitional cell carcinoma* of the endometrium is also rare, and metastatic disease from the bladder and ovary must be excluded during diagnosis (Ahluwalia, 2006).

PATTERNS OF SPREAD

Endometrial cancers have several different potential ways to spread beyond the uterus (Morrow, 1991). Type I endometrioid tumors and its variants spread most commonly, in order of frequency, by: (1) direct extension, (2) lymphatic metastasis, (3) hematogenous dissemination, and (4) intraperitoneal exfoliation. Type II serous and clear cell carcinomas have a particular propensity for extrauterine disease in a pattern that closely resembles epithelial ovarian cancer. In general, the various patterns of

spread are interrelated and often develop simultaneously.

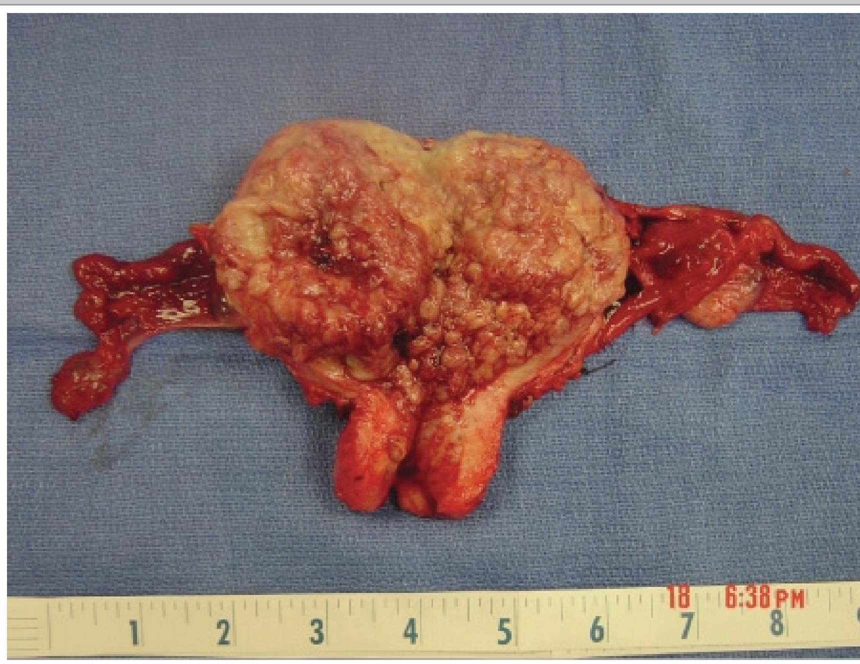
Invasion of the endometrial stroma and exophytic expansion within the uterine cavity follow initial growth of an early cancer (Fig. 33-16). Over time, the tumor invades the myometrium and ultimately may perforate the serosa (Table 33-6). Tumors situated in the lower uterine segment tend to involve the cervix early, whereas those in the upper corpus tend to extend to the fallopian tubes or serosa. Advanced regional growth may lead to direct invasion of adjacent pelvic structures, including the bladder, large bowel, vagina, and broad ligament.

Table 33-6 Correlation of Histologic Grade and Depth of Myometrial Invasion in Stage I Patients (n = 5,095)

Myometrial Invasion	Grade		
	1	2	3
None	29%	11%	15%
≤50%	51%	59%	46%
>50%	20%	30%	39%

Modified from Creasman, 2006, with permission.

FIGURE 33-16



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photograph of a uterine specimen with endometrioid adenocarcinoma. Tumor is seen filling the endometrial cavity and invading myometrial walls.

Lymphatic channel invasion and metastasis to the pelvic and para-aortic nodal chains can follow tumor penetration of the myometrium (Table 33-7). The lymphatic network draining the uterus is complex, and patients can have metastases to any single nodal group as well as combinations of groups (Burke, 1996). This haphazard pattern is in contrast to cervical cancer, in which

lymphatic spread usually follows a stepwise progression from pelvic to para-aortic to scalene nodal groups.

Table 33-7 Correlation of Histologic Grade and Depth of Myometrial Invasion with Risk of Nodal Metastases

	Pelvic Lymph Nodes			Para-aortic Lymph Nodes		
Myometrial Invasion	**G1**	**G2**	**G3**	**G1**	**G2**	**G3**
None	1%	7%	16%	<1%	2%	5%
≤50%	2%	6%	10%	<1%	2%	4%
>50%	11%	21%	37%	2%	6%	13%

Modified from Creasman, 2006, with permission.

Hematogenesis dissemination results most commonly in metastases to the lung and less commonly, to the liver, brain, bone, and other sites. Deep myometrial invasion is the strongest predictor of this pattern of spread (Mariani, 2001a).

Retrograde transtubal transport of exfoliated endometrial cancer cells is one mechanism by which malignant cells reach the peritoneal cavity. Serosal perforation of the tumor is another possible pathway. Most types of endometrial cancer cells found in the peritoneal cavity disappear within a short time and have low malignant potential (Hirai, 2001). Alternatively, in the presence of other high-risk features, such as adnexal metastases or serous histology, widespread intra-abdominal disease may result.

Treatment

SURGICAL STAGING

Women with endometrial cancer should undergo hysterectomy, BSO, and surgical staging using the FIGO system (Table 33-8). Almost three quarters of patients are stage I at diagnosis (Table 33-9). Only a few circumstances contraindicate primary surgery and include a desire to preserve fertility, massive obesity, high operative risk, and clinically unresectable disease. In general, an extrafascial ("simple") hysterectomy (see Section 41-19, Hysterectomy) is sufficient, but radical hysterectomy (see Section 43-1, Radical Abdominal Hysterectomy (Type III)) may be preferable for women with clinically obvious cervical extension of endometrial cancer (Cornelison, 1999; Mariani, 2001b). Vaginal hysterectomy with or without BSO is another option for those women who cannot undergo systematic surgical staging because of comorbidities (Orr, 2005).

Table 33-8 FIGO Surgical Staging System for Endometrial Cancer

FIGO Stage	Surgical-pathologic Findings
IA	Tumor limited to endometrium
IB	Tumor invades less than 50% of myometrium
IC	Tumor invades at least 50% of the myometrium
IIA	Tumor extends to the glandular epithelium of the endocervix
IIB	Tumor extends to the stromal connective tissue of the cervix
IIIA	Tumor involves serosa and/or adnexa (direct extension or metastasis) and/or cancer cells in ascites or peritoneal washings
IIIB	Vaginal involvement (direct extension or metastasis)
IIIC	Pelvic and/or paraaortic lymph node metastasis
IVA	Tumor invades bladder mucosa and/or bowel mucosa
IVB	Distant metastasis (i.e., inguinal nodes, omentum)

FIGO = International Federation of Gynecology Obstetrics.

From Benedet, 2000, with permission.

Table 33-9 Distribution of Endometrial Cancer by FIGO Stage (*n* = 7,990 Patients)

FIGO Stage	Percent
I	70
II	13
III	14
IV	3

FIGO = International Federation of Gynecology and Obstetrics.

From Creasman, 2006, with permission.

To manage a patient optimally, it is imperative to carefully review the histopathologic description of the preoperative biopsy findings. For example, papillary serous features should suggest the possibility of intraperitoneal disease in the upper abdomen that may make a vertical incision most appropriate (Orr, 2005). Traditionally, laparotomy has been the standard approach, but laparoscopic surgical staging is being used increasingly for endometrial cancer that appears clinically to be confined to the uterus.

Staging Laparotomy

Surgery begins with an adequate abdominal incision, most commonly vertical, but targeted to specific patient circumstances. On entering the peritoneal cavity, washings are obtained by pouring 50 to 100 mL of saline into the abdomen, manually circulating the fluid, and collecting it for cytologic assessment. Retrieval of ascitic fluid is a perfectly acceptable alternative, but ascites is encountered infrequently. Next, a thorough intra-abdominal and pelvic exploration is performed, and suspicious lesions are biopsied

or excised.

These preliminary procedures are followed by hysterectomy and BSO. The uterus is opened away from the operating table, and the depth of myometrial penetration may be determined by intraoperative gross examination or microscopic frozen section (Sanjuan, 2006; Vorgias, 2002). Historically, the combination of preoperative biopsy grade and intraoperative assessement of the depth of myometrial invasion were the two factors that a surgeon used to determine whether to proceed with lymph node dissection. However, recent studies have changed the paradigm.

This approach is inconsistent and frequently inadequate. It is difficult to predict with certainty the final histologic grade based on a preoperative biopsy or intraoperative frozen section (Eltabbakh, 2005). In addition, the depth of myometrial invasion determined in the operative room often is inaccurate. As a result, complete surgical staging with pelvic and para-aortic lymphadenectomy is recommended for *all* patients with endometrial cancer (see Sections 43-9, Pelvic Lymphadenectomy and 43-10, Para-Aortic Lymphadenectomy) (Frumovitz, 2004a, 2004b). At a minimum, any suspicious pelvic or para-aortic lymph nodes should be removed. Unfortunately, lymphatic mapping for a "sentinel" node does not appear to be a useful technique in endometrial cancer (see Chap. 31, Lymphadenectomy) (Frumovitz, 2007).

Higher nodal counts correlate with improved survival, most likely due to improved staging (Lutman, 2006). In addition, evidence suggests the possibility of a therapeutic benefit from multiple-site lymphadenectomy (Kilgore, 1995). Removal of grossly involved lymph nodes leads to a survival advantage (Havrilesky, 2005). Moreover, microscopic nodal disease may be resected unknowingly and prevent future relapse.

Patients with serous or clear cell features on preoperative biopsy should have extended surgical staging with an infracolic omentectomy and bilateral peritoneal biopsies of the pelvis, pericolic gutter, and diaphragm (see Section 43-12, Omentectomy) (Bristow, 2001a). As in ovarian cancer, a surgeon also should be prepared to resect any metastases (Bristow, 2000c).

Laparoscopic Staging

An alternative method of surgically staging combines a laparoscopic approach with both hysterectomy and lymphadenectomy (Ghezzi, 2006). In general, this approach is best suited to a select group of women with clinical stage I disease. However, laparoscopic pelvic and para-aortic lymph node dissection also may be an attractive option in women incompletely staged at their primary surgery (Childers, 1994).

The potential benefits of minimally invasive surgery are numerous. In general, patients have fewer blood transfusions, shorter hospital stays, lower perioperative morbidity, and better quality of life (Gil-Moreno, 2006; Zullo, 2005). Disadvantageously, surgical time typically is prolonged, exposure may be limited, limitations or bleeding may require conversion to laparotomy, and staging may be incomplete (Eitan, 2004; Spirtos, 2005). However, in selected patients, approximately 70 percent of planned cases can be completed successfully. Overall survival and recurrence rates in early reports are similar to those of a traditional abdominal approach (Magrina, 1999).

SURVEILLANCE

Most surgically treated patients simply can be followed by pelvic examination every 3 to 4 months for the first 2 years and twice yearly for an additional 3 years before returning to annual visits (Orr, 2005). Pap smears are not a mandatory part of surveillance because they identify an asymptomatic vaginal recurrence in less than 1 percent of patients and are not cost-effective (Bristow, 2006a; Cooper, 2006).

Women who have more advanced disease that requires postoperative radiation or chemotherapy or both warrant more aggressive monitoring. Serum CA125 measurements may be valuable, particularly for UPSC. Intermittent imaging using CT scanning or MR imaging also may be indicated. In general, the pattern of recurrent disease depends on the original sites of metastasis as well as the treatment received.

CHEMOTHERAPY

Paclitaxel (*T* axol), doxorubicin (*A* driamycin) and cisplatin (TAP) chemotherapy is the adjuvant treatment of choice for advanced endometrial cancer. In a randomized phase III GOG trial of 273 women (protocol 177), administration of seven courses of TAP was

superior to doxorubicin and cisplatin (AP), but toxicity was increasedâ€"particularly peripheral neuropathy (Fleming, 2004). A less toxic alternative to TAP chemotherapy is the combination of paclitaxel and carboplatin. Routinely used for the treatment of ovarian cancer, this regimen also has demonstrated efficacy in advanced-stage endometrial cancer (Hoskins, 2001; Sovak, 2006).

In practice, cytotoxic chemotherapy frequently is combined with radiotherapy in patients with advanced endometrial cancer. To reduce toxicity, directed pelvic or para-aortic radiation usually is employed rather than whole abdominal irradiation.

RADIATION

Primary Therapy

Primary radiation therapy usually is considered only in rare instances when a patient is an exceptionally poor surgical candidate. Intracavity brachytherapy such as Heyman capsules with or without external-beam pelvic radiation is the typical method (see Chap. 28, Brachytherapy). In general, the survival rate is 10 to 15 percent lower than that with surgical treatment (Chao, 1996; Fishman, 1996). These poor results suggest that a careful preoperative evaluation and appropriate consultation should be undertaken before denying any woman the benefits of hysterectomy (Orr, 2005).

Adjuvant Therapy

The use of postoperative radiation in women with stage I disease is highly controversial because of the low relapse rate and the scarcity of data from randomized trials. Most women with lower-risk surgical stage I disease may be counseled that postoperative radiation therapy can reduce the risk of recurrence in the vagina and pelvis. However, the cost and toxicity should be balanced against evidence that it does not improve survival or reduce distant metastasis (Creutzberg, 2001, 2004). In contrast, data do support treatment of women with stage IC, grade 3 endometrial adenocarcinoma with postoperative external beam pelvic radiotherapy (Aalders, 1980).

The efficacy of postoperative radiotherapy is even harder to decipher among women with surgical stage II endometrial adenocarcinoma. Most data consist of retrospective, single-institution experiences, and there is evidence to support external beam pelvic radiation, vaginal brachytherapy, both, or no further treatment (Ayhan, 2004; Calvin, 1999; Rittenberg, 2005). Currently, there is no standard approach, and most patients are treated individually based on analysis of coexisting risk factors (Feltmate, 1999).

In most women with stage III endometrial cancer, tumor-directed postoperative external beam radiation is indicated with or without chemotherapy (Schorge, 1996). Most commonly, radiation therapy is directed specifically at pelvic disease but may be extended to the para-aortic area if metastases are detected.

Few patients with stage IV disease are candidates for radiotherapy with curative intent. Infrequently, a locally confined stage IVA tumor may be an exception. With stage IVB disease, intraperitoneal metastases most often lie outside a directed radiation field. Therefore, whole abdominal irradiation generally is not preferable to chemotherapy. As a result, the role of radiotherapy generally is palliative in these women (Goff, 1994).

HORMONAL THERAPY

Primary Treatment

One of the unique characteristics of endometrial cancer is its hormone responsiveness. Rarely, progestin is used for primary treatment of women with excessively high operative risk. This may be the only feasible palliative option in a few exceptional circumstances. In other uncommon situations of clinical stage I disease and grade 1 adenocarcinoma in a poor surgical candidate, an intrauterine progestational device may be useful. In general, this strategy should be used with great caution (Dhar, 2005; Montz, 2002).

Adjuvant Hormonal Therapy

Single-agent progestins have shown activity in women with advanced disease (Lentz, 1996; Thigpen, 1999). Tamoxifen modulates the expression of the progesterone receptor and is postulated to thereby improve progestin efficacy. Clinically, high response rates have been noted with tamoxifen used adjunctively with progestin therapy (Fiorica, 2004; Whitney, 2004). In general, toxicity is very low, but this combination is used most commonly for recurrent disease.

Estrogen-Replacement Therapy

Because of the presumed role of excess estrogen in the development of endometrial cancer, there has been great concern historically that use of estrogen in women with known endometrial cancer feasibly could increase the risk of recurrence or death. However, such an effect has not been observed (Suriano, 2001). The GOG attempted to determine the effect of estrogen-replacement therapy by randomly assigning 1,236 women who had undergone surgery for stage I and II endometrial cancer to receive either estrogen or placebo. Although the study did not meet its enrollment goals, the low recurrence rate (2 percent) was promising (Barakat, 2006). Due to the potential risks and lack of proven safety, women should be counseled carefully before beginning a regimen of postoperative estrogen.

MANAGEMENT OF UTERINE PAPILLARY SEROUS CARCINOMA

This most aggressive type of endometrial carcinoma is rare, and thus, randomized trials are difficult to perform. As a result, most data are single-institution, retrospective analyses. Treatment usually is individualized but often very different from that for typical endometrioid adenocarcinoma.

When a preoperative biopsy demonstrates serous features, it is imperative to perform comprehensive surgical staging for UPSC. This includes total abdominal hysterectomy, BSO, peritoneal washings, pelvic/para-aortic nodal dissection, infracolic omentectomy, and peritoneal biopsies (Chan, 2003). Even noninvasive disease often is widely metastatic (Gehrig, 2001). Fortunately, patients tend to have a good prognosis if surgical staging confirms that disease is confined to the uterus (stage Iâ€"II) (Grice, 1998).

Occasionally, no residual UPSC is evident on the hysterectomy specimen, or the tumor minimally involves the tip of a polyp. These women with surgical stage IA can be observed safely. However, all other patients with stage I disease should be considered for adjuvant treatment. One effective strategy is to treat women with stage I disease postoperatively using paclitaxel and carboplatin for three to six cycles along with concomitant vaginal brachytherapy (Dietrich, 2005; Kelly, 2005). However, some data suggest an intrinsic radioresistance for UPSC tumors (Martin, 2005). Moreover, based on the largest reported retrospective review of surgical stage I patients, Huh and colleagues (2003) questioned the benefit of any radiation therapy.

Women with stage II UPSC are more likely to benefit from pelvic radiotherapy with or without chemotherapy. Those having stage III disease are especially prone to have recurrent disease at distant sites. Accordingly, paclitaxel and carboplatin should be considered in addition to tumor-directed radiotherapy (Bristow, 2001a; Slomovitz, 2003).

In practice, many patients will have stage IVB disease. Aggressive surgical cytoreduction is perhaps most important because one of the strongest predictors of overall survival is the amount of residual disease. Postoperatively, at least six cycles of paclitaxel and carboplatin chemotherapy are indicated (Bristow, 2001b; Moller, 2004). Alternatively, enrollment in a clinical trial such as GOG protocol 209 is another option if the woman is eligible.

FERTILITY-SPARING MANAGEMENT

Hormonal therapy without hysterectomy is an option in carefully selected young women with endometrial cancer who desperately wish to preserve their fertility. In general, this strategy should apply only to those with grade 1 adenocarcinomas (type I tumors) and with no imaging evidence of myometrial invasion. Rarely, women with grade 2 lesions may be considered candidates, although it may be advisable to further assess the disease laparoscopically (Morice, 2005). The aim of hormonal treatment is to reverse the lesion, but obviously, any type of medical management involves inherent risk of disease progression that a patient should be willing to accept (Yang, 2005).

Progestins are the most commonly used agents. Megestrol acetate, 160 mg given orally daily, has demonstrated efficacy. Alternatively, MPA may be delivered by oral or intramuscular administration at varying doses (Gotlieb, 2003a). Combinations of progestin therapy with tamoxifen and gonadotropin-releasing hormone (GnRH) agonists are used less frequently (Wang, 2002). Regardless of the hormonal agent, recurrence rates are high during long-term observation (Gotlieb, 2003b; Niwa, 2005).

Women receiving fertility-sparing conservative management must be monitored carefully by repeated endometrial biopsy or D&C every 3 months to assess treatment efficacy. If there is evidence of persistence, then a regimen may need to be changed or the dose increased. Hysterectomy and operative staging should be recommended if a lesion does not regress with hormonal therapy or

if disease progression is suspected.

Delivery of a healthy infant is a feasible expectation for women who respond to treatment and have normal histologic findings in surveillance endometrial samplings. However, assisted reproductive technologies may be required to achieve pregnancy in some of these women (see Chap. 20, Unexplained Infertility). Postpartum, patients again should be monitored regularly for recurrent endometrial adenocarcinoma (Ferrandina, 2005). In general, women should undergo hysterectomy at completion of childbearing or whenever the preservation of fertility is no longer desired.

Prognostic Factors

Many clinical and pathologic factors influence the likelihood of endometrial cancer recurrence and survival (Table 33-10). Of these, FIGO surgical stage is the most important overriding variable because it incorporates many of the most important risk factors (Table 33-11). Metastatic disease to the adnexa, pelvic/para-aortic lymph nodes, and peritoneal surfaces is reflected by FIGO stage.

Table 33-10 Poor Prognostic Variables in Endometrial Cancer
Advanced surgical stage
Older age
Histologic type: UPSC or clear cell adenocarcinoma
Advanced tumor grade
Presence of myometrial invasion
Presence of lymphovascular space invasion
Peritoneal cytology positive for cancer cells
Increased tumor size
High tumor expression levels of ER and PR

ER = estrogen receptor; PR = progesterone receptor; UPSC = uterine papillary serous carcinoma.

Table 33-11 Endometrial Cancer 5-Year Survival Rates for Each Surgical Stage (*n* = 8,100 Patients)

FIGO Stage	Survival (%)
IA	91
IB	91
IC	85
IIA	83
IIB	66
IIIA	50
IIIB	50
IIIC	57
IVA	25
IVB	20

FIGO = International Federation of Gynecology and Obstetrics.

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Relapse

Patients with recurrent endometrial cancer generally require individualized treatment. In general, the site of relapse is the most important predictor of survival. Depending on the circumstances, surgery, radiation, chemotherapy, or a combination of modalities may be the best strategy. The most curable scenario is an isolated relapse at the vaginal apex in a previously unirradiated patient. These women usually are treated effectively by external beam pelvic radiotherapy. In patients who were irradiated previously, exenteration is often the only curative option (see Section 43-3, Total Pelvic Exenteration) (Barakat, 1999; Morris, 1996). Nodal recurrences or isolated pelvic disease is more likely to result in progressive disease regardless of treatment modality. However, both are often appropriate indications for external-beam radiotherapy. Salvage cytoreductive surgery also may be beneficial in selected patients (Awtrey, 2006; Bristow, 2006b).

Widely disseminated endometrial cancer or a relapse not amenable to radiation or surgery is an indication for systemic chemotherapy. Such patients should be enrolled in an experimental trial, if possible, due to the limited duration of response and the urgent need for more effective therapy. Currently, TAP is thought to be the most active cytotoxic regimen (Fleming, 2004). Paclitaxel and carboplatin is another useful combination that is being compared with TAP in GOG protocol 209. Progestin therapy with or without tamoxifen is a less toxic option that is particularly useful in selected patients (Fiorica, 2004; Whitney, 2004).

In general, effective palliation of women with incurable, recurrent endometrial cancer requires an ongoing dialogue to achieve the optimal balance between symptomatic relief and treatment toxicity.

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UTERINE SARCOMA: INTRODUCTION

Malignant tumors of the uterine corpus are broadly divided into three main types: carcinomas (see Chap. 33), sarcomas, and carcinosarcomas. Although the latter two categories are rarely encountered, they tend to behave more aggressively and contribute to a disproportionate number of uterine cancer deaths. Pure sarcomas are characterized mainly by differentiation toward smooth muscle (leiomyosarcoma) or toward stromal tissue within the endometrium (endometrial stromal tumors). Carcinosarcomas are mixed tumors demonstrating both epithelial and stromal components and are also known as *malignant mixed mÃ¼llerian tumors* (MMMTs). In general, uterine sarcomas grow quickly, lymphatic or hematogenous spread occurs early, and the overall prognosis is poor. However, there are several notable exceptions among these tumors.

EPIDEMIOLOGY AND RISK FACTORS

Although sarcomas commonly have been thought to account for fewer than 5 percent of all cancers of the uterine corpus, recent studies suggest that they may comprise up to 8 percent (Brooks, 2004; Greer, 2006). In most studies, MMMT is the most prevalent subtype, accounting for about half of sarcomas, followed closely by leiomyosarcomas. Endometrial stromal tumors are uncommon and comprise less than 10 percent of all cases.

Because of the small number of these tumors, the epidemiology of uterine sarcomas has not been studied extensively. As a result, relatively few risk factors have been identified, but they include chronic excess estrogen exposure, tamoxifen use, African-American race, and prior pelvic radiation. In contrast, combination oral contraceptive pill use and smoking appear to lower the risk for these tumors.

PATHOGENESIS

Several of the identifiable risk factors for uterine sarcoma parallel those observed in endometrial carcinoma. Thus, it would seem plausible that these tumors have a similar pathogenesis. However, their morphologic diversity suggests a variety of potential pathways. For example, inactivation of the *PTEN* tumor suppressor gene is a common early event in typical type I endometrioid adenocarcinomas. These mutant clones then may undergo selective unregulated proliferation when exposed to an environment of unopposed estrogen. However, among uterine sarcomas, *PTEN* mutations are observed with any frequency in MMMTs only in endometrioid-type components (Amant, 2002). For most sarcomas, uniquely different pathways have been proposed.

Leiomyosarcomas have a monoclonal origin. Although commonly believed to arise from benign leiomyomas, for the most part, they do not. Instead, they appear to develop de novo as solitary lesions (Zhang, 2006). Supporting this theory, leiomyosarcomas have molecular pathways that have been shown to be distinct from leiomyomas or normal myometrium (Quade, 2004; Skubitz, 2003).

In endometrial stromal tumors, chromosomal aberrations are heterogeneous (Halbwedl, 2005). However, the pattern of rearrangements is clearly nonrandom, and chromosomal arms 6p and 7p are involved frequently (Micci, 2006). A loss of tumor suppressor gene function(s) is suspected, however, relatively few cases have been studied to generate a working hypothesis (Moinfar, 2004).

In general, uterine MMMTs are also monoclonal neoplasms (Wada, 1997). Therefore, both the carcinoma and sarcoma components are thought to arise from a common epithelial progenitor cell. Acquisition of any number of genetic mutations, including defects in the *p53* tumor suppressor gene and DNA mismatch repair gene, may be sufficient to trigger tumorigenesis. These early molecular defects will be shared by both components as the tumor undergoes divergent carcinomatous and sarcomatous differentiation.

Thereafter, acquired molecular defects will be discordant between the two components (Taylor, 2006). This genetic progression and subsequent diversion parallel the varying phenotypes observed in these tumors (Fujii, 2000).

DIAGNOSIS

Signs and Symptoms

As in endometrial cancer, abnormal vaginal bleeding is the most frequent presenting symptom for all histologic types of uterine sarcoma (see Chap. 8, Diagnosis) (Gonzalez-Bosquet, 1997). Moreover, women with uterine sarcoma also commonly complain of pelvic or abdominal pain. Up to a third of women will describe significant discomfort that may result from passage of clots, rapid uterine enlargement, or prolapse of a sarcomatous polyp through an effaced cervix (De Fusco, 1989). In addition, a profuse, foul-smelling discharge may be obvious. Gastrointestinal and genitourinary complaints are also common. It is worth noting that degenerating leiomyomas with necrosis can mimic all these sign and symptoms.

Due to rapid growth, a uterus may extend out of the pelvis into the middle or upper abdomen. Although uterine sarcomas tend to grow quickly, no criteria define what constitutes significant growth. Fortunately, the incidence of uterine sarcoma in such cases is extremely low (<0.5 percent), and in most instances, benign enlarging leiomyomas are found (Leibsohn, 1990; Parker, 1994).

Despite these often dramatic presentations, many women with uterine sarcoma will have few symptoms other than abnormal vaginal bleeding and a seemingly normal uterus on physical examination.

Endometrial Sampling

The sensitivity of an office endometrial biopsy or dilatation and curettage (D&C) to detect uterine sarcoma is lower than that for endometrial carcinomas. For most women with MMMT, sampling will lead to a correct diagnosis, although in many cases only the carcinomatous features are evident. The reverse is also true, and occasionally, a uterine MMMT is suspected based on endometrial biopsy findings, but no sarcomatous features are found within a hysterectomy specimen.

Symptomatic women with leiomyosarcoma receive a correct diagnosis in only 25 to 50 percent of cases. This probably is related to the origin of these neoplasms in the myometrium rather than the endometrium. Similarly, endometrial stromal nodules and sarcomas may be undetectable by pipelle biopsy, especially if the neoplasm is entirely intramural (Yang, 2002; Zaloudek, 1994).

Laboratory Testing

In selected patients, serum CA125 levels may be a somewhat useful marker of disease response. However, elevated levels usually do not directly reflect tumor burden, and as a result, the utility of the test is limited (Holcomb, 1999).

Imaging Studies

Unlike most women with endometrial carcinoma, who require only a preoperative chest radiograph, additional imaging studies often are helpful if sarcoma is diagnosed before hysterectomy. In most cases, a computed tomographic (CT) scan of the abdomen and pelvis should be performed routinely. This serves at least two purposes. First, sarcomas often violate normal soft tissue planes in the pelvis, and therefore, unresectable tumors can be identified preoperatively. Second, extrauterine metastases may be visualized. In either case, treatment may be altered based on radiographic findings.

If a diagnosis is still in question, magnetic resonance (MR) imaging is most useful for distinguishing uterine sarcoma from a benign "mimic". For example, MR imaging can assist in reliably determining whether a pedunculated mass is a submucosal leiomyoma or a prolapsing endometrial stromal tumor (Kido, 2003). As a diagnostic tool for sarcoma, sonography is far less helpful. Positron-emission tomography (PET) scanning is used most effectively for disease monitoring after completion of treatment.

Role of the Generalist

Preoperative consultation with a gynecologic oncologist is recommended for any patient with a biopsy suggesting uterine sarcoma. The potential for intra-abdominal metastases and disruption of tissue planes within the pelvis increases the technical difficulty and surgical risks. More important, the approach to staging is often subtly dissimilar to that of endometrial carcinomas. For example, because of the low rate of metastasis, it may be appropriate to sample only suspicious nodes for leiomyosarcomas instead of

performing a complete pelvic and para-aortic lymphadenectomy. In addition, it may be prudent to preserve the ovaries in a young woman with an endometrial stromal tumor because the risk of adnexal metastasis is minimal. In general, a treatment plan is best organized preoperatively, if possible.

Many uterine sarcomas are not diagnosed until surgery or several days later when a pathology report is available. As a result, unstaged cases are common, and a gynecologic oncologist should be consulted at the earliest feasible time. If the diagnosis is made postoperatively, the decision to proceed with surveillance only, reoperation, or radiotherapy varies widely depending on the type of sarcoma and other circumstances. In general, these options are less straightforward than in typical endometrial carcinomas largely because of the rarity of these tumors and the comparatively limited data supporting one strategy compared with another.

PATHOLOGY

Uterine mesenchymal tumors are classified broadly into pure and mixed tumors (Table 34-1). Pure sarcomas are virtually all homologous, differentiating into mesenchymal tissue that is normally present within the uterus, such as smooth muscle (leiomyosarcoma) or stromal tissue within the endometrium (endometrial stromal tumors). Pure heterologous sarcomas, are those composed of tissue unlike that in which it developed. These, such as uterine chondrosarcoma, are exceedingly rare.

Table 34-1 World Health Organization Histologic Classification of Mesenchymal Tumors of the Uterus
Pure mesenchymal tumors
Smooth muscle tumors
Leiomyoma, including histologic and growth-pattern variants
Leiomyosarcoma
Smooth muscle tumor of uncertain malignant potential (STUMP)
Endometrial stromal tumors
Endometrial stromal nodule
Endometrial stromal sarcoma
High-grade undifferentiated sarcoma
Mixed epithelial and mesenchymal tumors
Malignant mixed mullerian tumor (carcinosarcoma)
Adenosarcoma

From Hendrickson, 2003, and McCluggage, 2003, with permission.

Mixed sarcomas contain a malignant mesenchymal component admixed with an epithelial element. If the epithelial element is malignant, the tumor is termed *carcinosarcoma* or *MMMT.* If the element is benign, the term *adenosarcoma* is used. The mesenchymal component of MMMTs can be either homologous or heterologous, reflecting the potentiality of the uterine primordium.

Leiomyosarcoma

Leiomyosarcomas account for about 30 to 40 percent of uterine sarcomas and 1 to 2 percent of all uterine malignances. The average age at presentation is the early 50s, and only 15 percent develop in women younger than 40 years. Most tumors (60

percent) are stage I at the time of diagnosis. Stage II (10 percent), stage III (10 percent), and stage IV (20 percent) disease comprise the remainder (Giuntoli, 2003).

The histopathologic criteria for diagnosing leiomyosarcoma is somewhat controversial but includes the frequency of mitotic figures, the extent of nuclear atypia, and the presence of any coagulative tumor cell necrosis (Table 34-2 and Fig. 34-1). Occasionally, a leiomyosarcoma will be reported as low, intermediate, or high grade, but the overall utility of grading is controversial, and no universally accepted grading system exists. In most cases, the mitotic index exceeds 15 mitotic figures per 10 high-power fields, moderate to severe cytologic atypia is seen, and tumor cell necrosis is prominent (Hendrickson, 2003; Zaloudek, 1994).

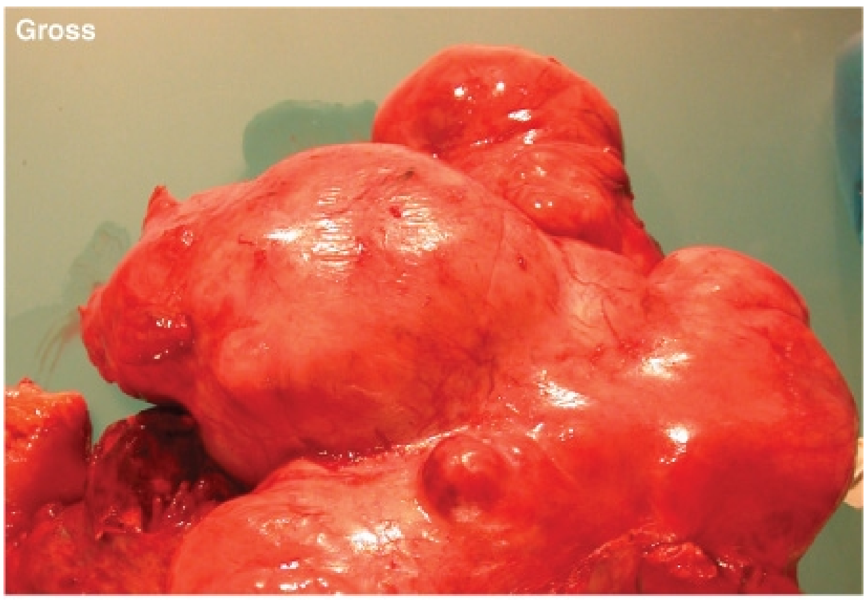
Table 34-2 Diagnostic Criteria for Uterine Leiomyosarcoma

Coagulative tumor cell necrosis	Mitotic Index	Degree of Atypia
Present	≥10 MF/10 HPF	None
	Any	Diffuse, significant
Absent	≥10 MF/10 HPF	Diffuse, significant

MF/10 HPF = mitotic figure(s) per 10 high-power fields.

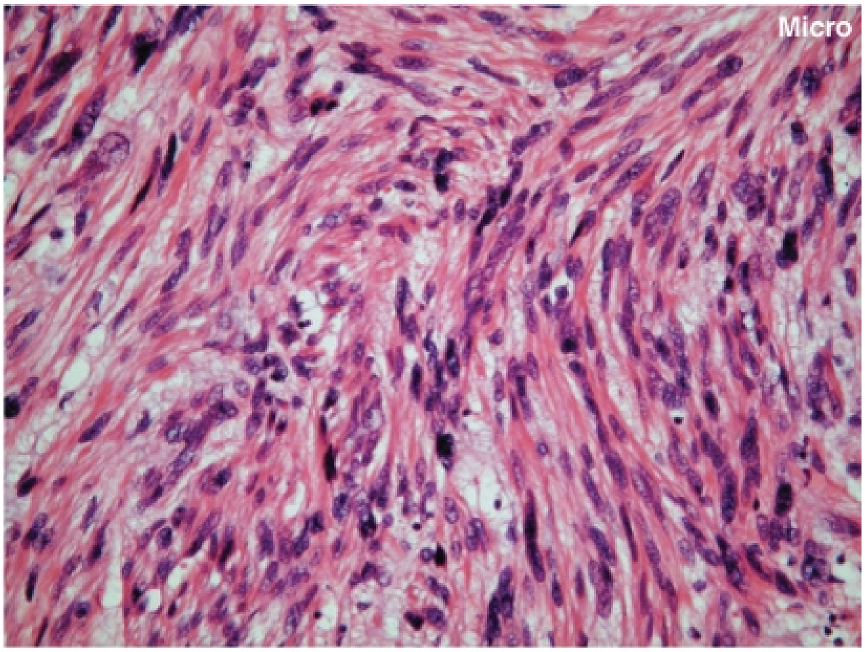
From Hendrickson, 2003, with permission.

FIGURE 34-1



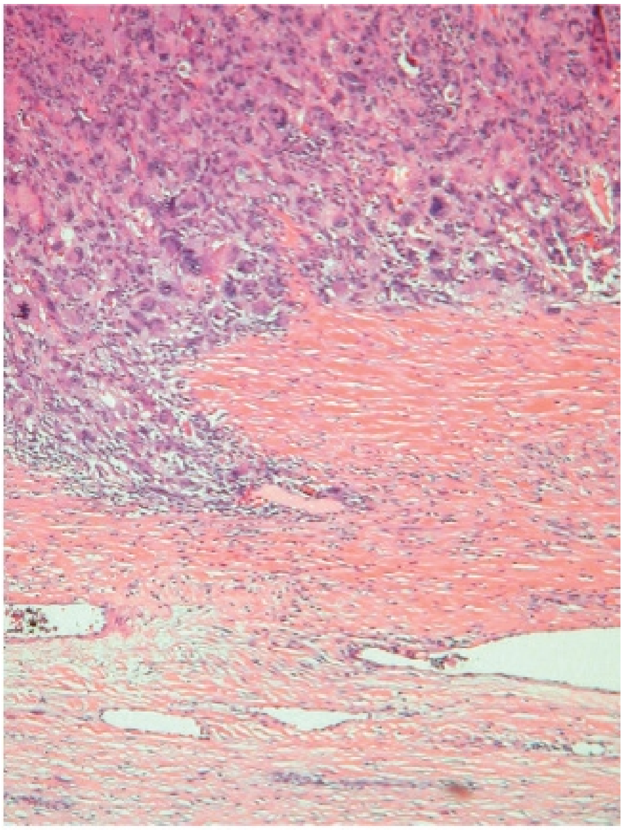
A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



C

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Leiomyosarcoma. **A.** Photograph displays a gross specimen of this tumor. **B.** Photomicrograph of leiomyosarcoma. In contrast to leiomyomas, leiomyosarcomas are cellular, with nuclear atypia and increased mitoses. **C.** High-grade pleomorphic sarcomas can have bizarre nuclei and mitoses and invade the myometrium. *(Courtesy of Dr. Raheela Ashfaq.)*

SMOOTH MUSCLE TUMOR OF UNCERTAIN MALIGNANT POTENTIAL (STUMP)

Tumors that cannot be diagnosed reliably as benign or malignant based on generally applied criteria fall into this category. The diagnosis should be used sparingly and is reserved for smooth muscle neoplasms whose appearance is ambiguous (Hendrickson, 2003).

Endometrial Stromal Tumors

Significantly less common than leiomyosarcomas or uterine MMMTs, endometrial stromal tumors comprise fewer than 10 percent of all uterine sarcomas. Patients typically are diagnosed in their late 40s and early 50s, younger than women developing other uterine malignancies. Although constituting a wide morphologic spectrum, endometrial stromal tumors are composed exclusively of cells that resemble the endometrial stroma and include both benign stromal nodules and malignant stromal tumors.

Historically, there has been controversy about subdivision of these tumors. Recently, the division of endometrial stromal sarcomas into low- and high-grade categories has fallen out of favor. In its place, the designation *endometrial stromal sarcoma* is now best restricted to neoplasms that formerly were referred to as low grade. Alternatively, the term *high-grade undifferentiated sarcoma* is believed to more accurately reflect those tumors without recognizable evidence of a definite endometrial stromal phenotype. These lesions are almost invariably high grade and often resemble the mesenchymal component of a uterine MMMT (Oliva, 2000). In this revised classification, the distinctions are not determined by mitotic count but rather on features such as nuclear pleomorphism and necrosis (Evans, 1982; Hendrickson, 2003).

ENDOMETRIAL STROMAL NODULE

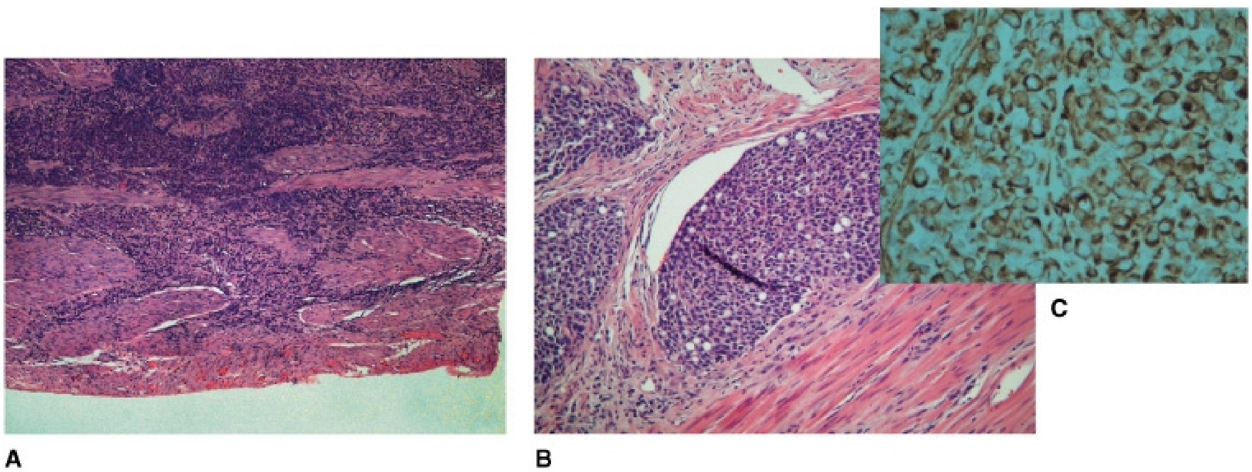
Representing less than a quarter of endometrial stromal tumors, these rare nodules are benign, characterized by a well-delineated margin, and composed of neoplastic cells that resemble proliferative-phase endometrial stromal cells. Grossly, the tumor is a solitary, round or oval, fleshy nodule measuring a few centimeters. Histologically, they are distinguished from endometrial stromal sarcomas by a lack of myometrial infiltration (Dionigi, 2002). These nodules are benign, and myomectomy is an appropriate option. However, because differentiation between endometrial stromal sarcoma and this benign lesion cannot be determined clinically, it is important to remove the entire nodule. Thus, for large lesions, hysterectomy may be required (Hendrickson, 2003).

ENDOMETRIAL STROMAL SARCOMA

The precise frequency of these tumors is difficult to estimate because they are excluded from some reports and included in others, and the terminology used has been inconsistent. In general, endometrial stromal sarcomas (formerly called *low grade*) are thought to be the most frequently encountered stromal tumor variant and are twice as common as high-grade undifferentiated sarcomas.

Most commonly, they extensively invade the myometrium and extend to the serosa in about half of cases. Less often, they present as a solitary, well-delineated, predominantly intramural mass that is difficult to distinguish grossly from an endometrial stromal nodule. Microscopically, endometrial stromal sarcomas resemble the stromal cells of proliferative-phase endometrium (Fig. 34-2).

FIGURE 34-2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photomicrograph of endometrial stromal sarcoma. **A.** Endometrial stromal type cells infiltrate the myometrium. **B.** The tumor often plugs the uterine vasculature and is CD10-positive (**C**). CD10 is a immunohistochemical marker of normal endometrial stroma. Staining is found in endometrial stromal nodules and endometrial stromal sarcoma. When strong and diffuse, CD10 staining may be useful in distinguishing these tumors from histological mimics. *(Courtesy of Dr. Raheela Ashfaq.)*

Metastases are rarely detected prior to diagnosis of the primary lesion. However, permeation of the lymphatic and vascular channels is characteristic. In up to a third of cases, extrauterine extension is present, often appearing as worm-like plugs of tumor within the vessels of the broad ligament and adnexa. At operation, this may resemble intravenous leiomyomatosis or a broad ligament leiomyoma, but frozen-section analysis usually can make the distinction (see Chap. 9, Leiomyomatosis).

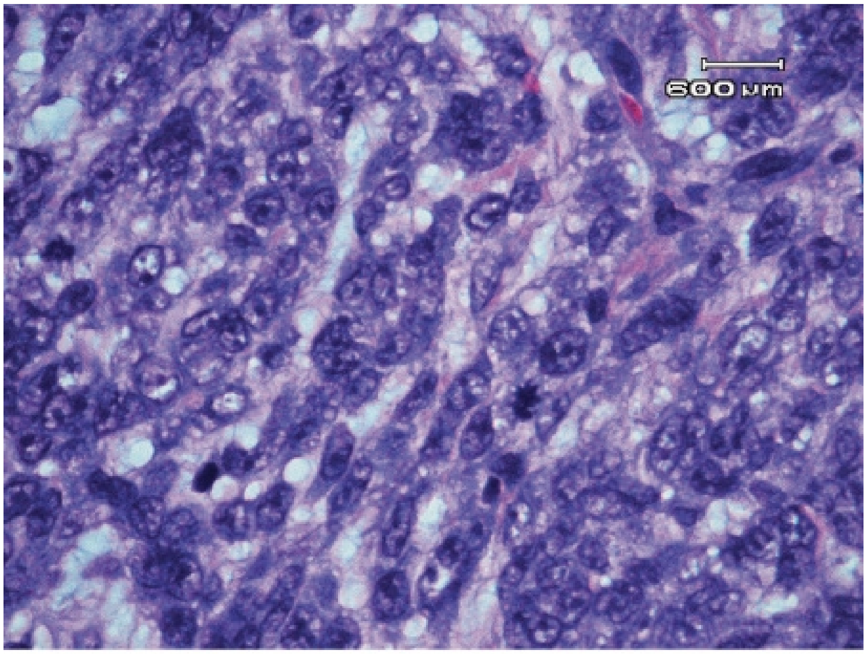
HIGH-GRADE UNDIFFERENTIATED SARCOMA

Compared with endometrial stromal sarcomas, these tumors tend to be larger and more polypoid, often filling the uterine cavity. Instead of an infiltrating pattern, high-grade undifferentiated sarcomas displace the myometrium more destructively, leading to prominent hemorrhage and necrosis.

Microscopically, the cells are larger and more pleomorphic. The presence of marked cellular atypia is characteristic (Fig. 34-3).

Typically, there are greater than 10 mitoses per 10 high-power fields, but frequently there are more than 20 in the most active areas. These tumors lack specific differentiation and bear no histologic resemblance to endometrial stroma (Hendrickson, 2003; Zaloudek, 1994).

FIGURE 34-3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photomicrograph of high-grade undifferentiated sarcoma. High-grade sarcomas usually have anaplastic nuclei with high numbers of atypical mitoses. *(Courtesy of Dr. Raheela Ashfaq.)*

Malignant Mixed MÃ¼llerian Tumor (MMMT)

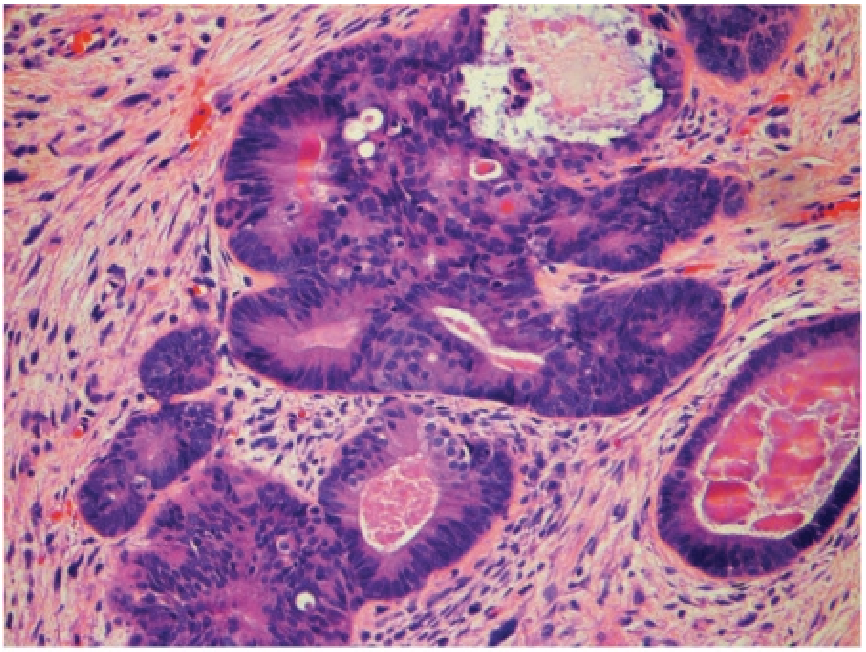
Accumulating clinical and pathologic evidence suggests that MMMTs actually represent endometrial carcinomas that have undergone clonal evolution, resulting in the acquisition of sarcomatous features. In principle, these tumors are metaplastic carcinomas. Clinically, their pattern of spread more closely mirrors that of aggressive endometrial carcinomas than that of sarcomas. In addition, metastases usually show carcinomatous elements (with or without sarcomatous differentiation).

However, by convention, MMMTs are grouped with uterine sarcomas and account for about half of all these tumors. Of all uterine malignancies, about 2 to 3 percent are MMMTs. Patients are often elderly, having an average age of 65 years. Less than 5 percent are diagnosed in women younger than 50 years. Most cancers (40 percent) are stage I at the time of diagnosis. Stage II (10 percent), stage III (25 percent), and stage IV (25 percent) disease make up the remainder (Sartori, 1997; Vaidya, 2006).

Grossly, the tumor is sessile or polypoid, bulky, necrotic, and often hemorrhagic. It often fills the endometrial cavity and deeply invades the myometrium. In classic cases, a large tumor protrudes through the external cervical os and fills the vaginal vault.

Microscopically, MMMTs have an admixture of epithelial and mesenchymal differentiation. The malignant epithelial element is typically an adenocarcinoma of endometrioid type, but serous, clear cell, mucinous, squamous cell, and undifferentiated carcinomas are also common (Fig. 34-4) (see Table 33-4). Mesenchymal components can be homologous, usually resembling endometrial stromal sarcomas or fibrosarcomas. Alternatively, heterologous mesenchymal differentiation can be found in association with areas of endometrial stromal or undifferentiated sarcomas. Most commonly, rhabdomyosarcoma or chondrosarcoma comprises these cases of heterologous mesenchymal differentiation (Fig. 34-5). There is no clinical importance to designating a uterine MMMT as homologous or heterologous (McCluggage, 2003; Zaloudek, 1994).

FIGURE 34-4



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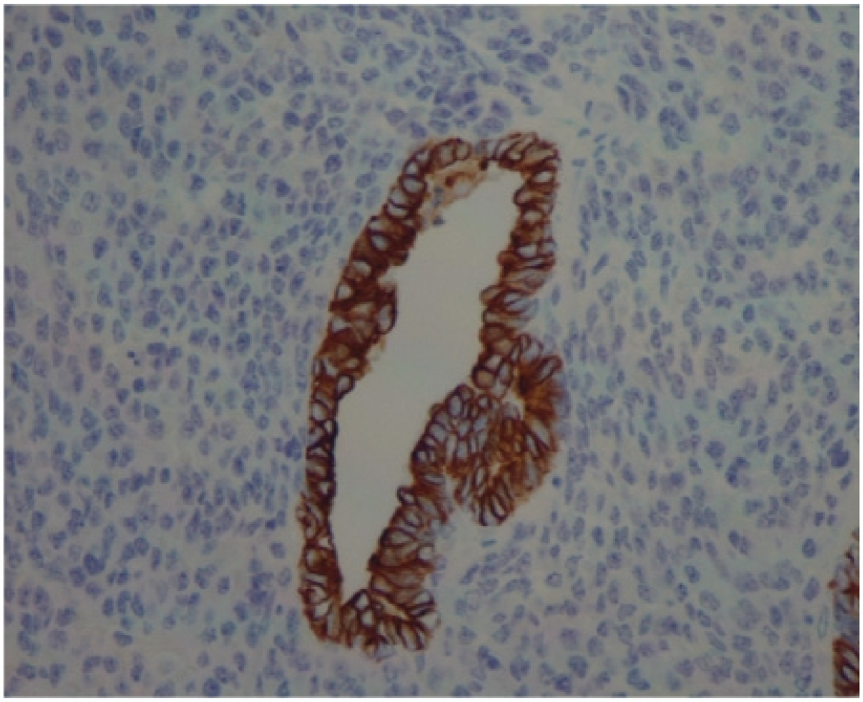

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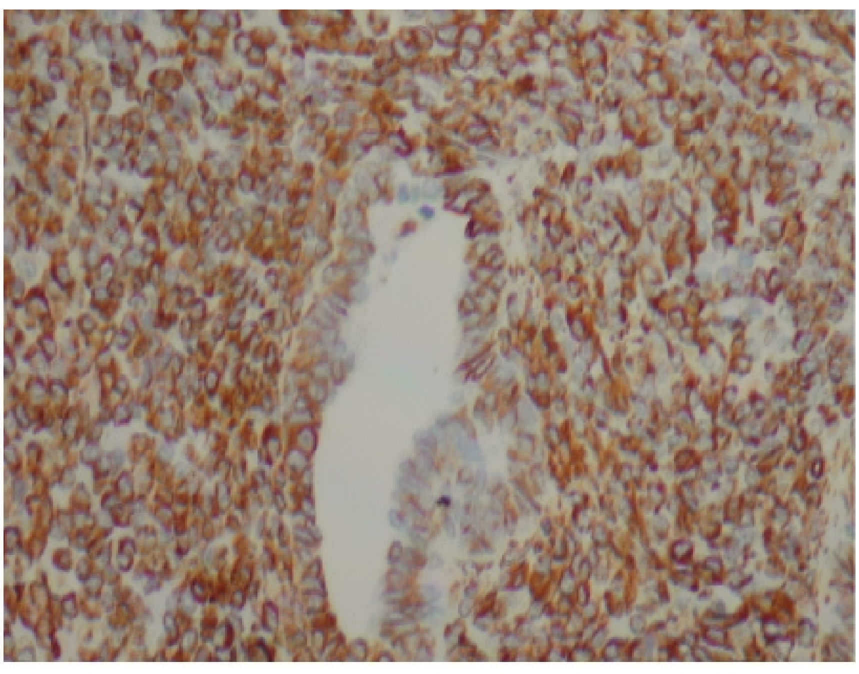
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

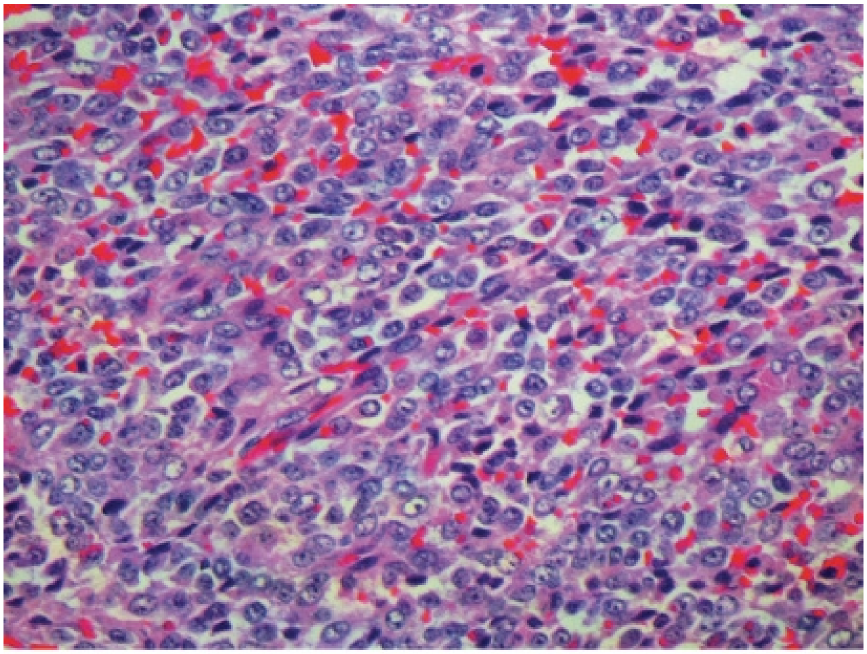


C

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photomicrograph of malignant mixed mÃ¼llerian tumor (MMMT). **A.** In MMMT, both the glands and the stroma are malignant. **B.** This is highlighted by epithelial markers such as keratin, which stains strongly positive in glands but not in the malignant stroma. **C.** Conversely, the stroma stains strongly with vimentin, a stromal marker. *(Courtesy of Dr. Raheela Ashfaq.)*

FIGURE 34-5



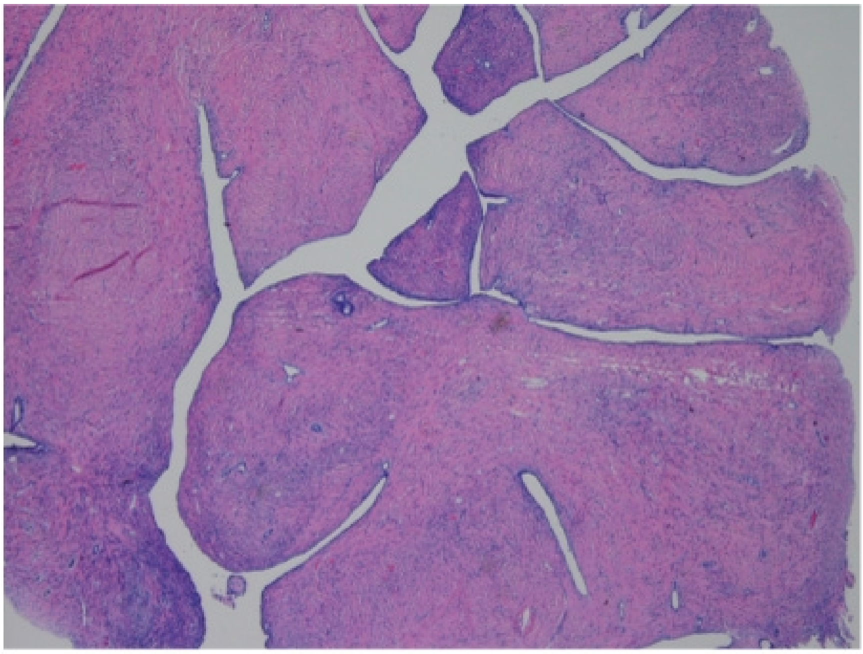
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photomicrograph of malignant mixed mÃ¼llerian tumor (MMMT). These tumors can have heterologous elements that may include rhabdomyosarcoma (as shown), chondrosarcoma, osteosarcoma, or liposarcoma. *(Courtesy of Dr. Raheela Ashfaq.)*

Adenosarcoma

These rare biphasic neoplasms are characterized by a benign epithelial component and a sarcomatous mesenchymal component. They may develop in women of all ages. Grossly, adenosarcomas grow as exophytic polypoid masses that extend into the uterine cavity. Rarely, they may arise in the myometrium, presumably from adenomyosis. Microscopically, isolated glands are dispersed throughout the mesenchymal component and often are dilated or compressed into thin slits (Fig. 34-6). Typically, the mesenchymal component resembles an endometrial stromal sarcoma or fibrosarcoma and contains varying amounts of fibrous tissue and smooth muscle.

FIGURE 34-6



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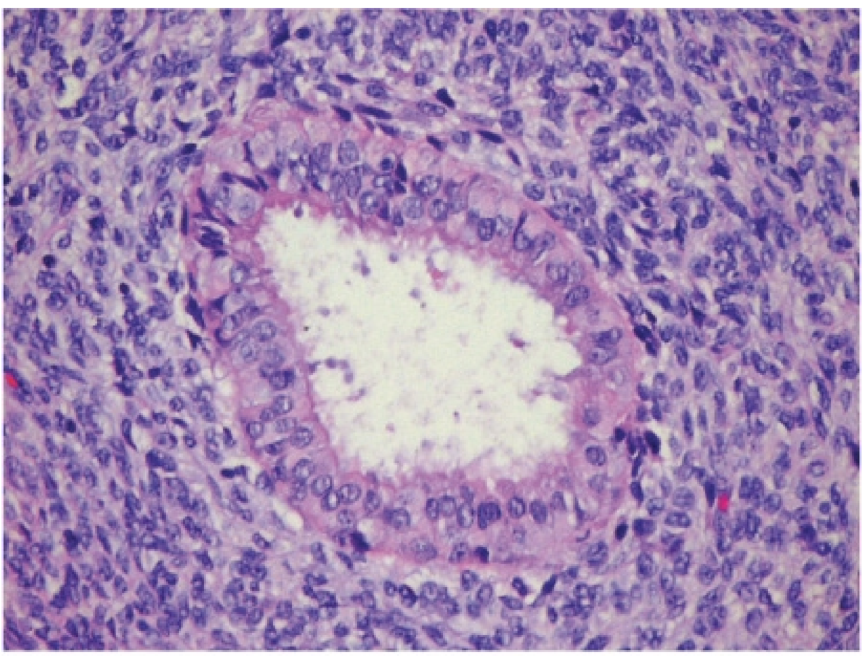
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photomicrograph of adenosarcoma. **A.** A broad-based villous architecture is seen typically at low magnification. **B.** Normal endometrial glands are surrounded by a cellular stroma consisting of a low-grade sarcomaâ€”in this case, an endometrial stromal sarcoma. *(Courtesy of Dr. Raheela Ashfaq.)*

In general, these are considered low-grade tumors with mild atypia and relatively few mitotic figures. However, 10 percent have a more malignant behavior due to one-sided proliferation of the sarcomatous, often high-grade component. These adenosarcomas are designated as having "sarcomatous overgrowth", and patients have a poor prognosis, similar to that of MMMTs (Krivak, 2001; McCluggage, 2003).

PATTERNS OF SPREAD

Uterine sarcomas generally fall into two categories of malignant behavior. First, leiomyosarcomas, high-grade undifferentiated sarcomas, and MMMTs are consistently characterized by an aggressive growth pattern, early lymphatic or hematogenous dissemination, and rapid disease progression despite treatment. In contrast, endometrial stromal sarcomas and adenosarcomas have an indolent growth pattern with long disease-free intervals. All these tumors grow, to some degree, by direct extension.

Leiomyosarcomas have a propensity for hematogenous dissemination. For example, lung metastases are particularly common, and more than half of patients will have distant spread when diagnosed with recurrent disease. To a lesser extent, leiomyosarcomas metastasize via lymphatic channels. In a clinicopathologic Gynecologic Oncology Group (GOG) study, fewer than 5 percent of clinical stage I and II patients had nodal involvement (Major, 1993).

The opposite is true for MMMTs, in which half of patients with clinically stage I tumors will have nodal metastases. Extra-abdominal spread is less common, and most recurrences are found in the pelvis or abdomen.

STAGING

There is no specific staging system for uterine sarcomas due to their rarity. Tumors were classified initially by criteria modified from the clinical staging system for endometrial carcinoma (Table 34-3). Currently, however, most clinicians use the International Federation of Gynecology and Obstetrics (FIGO) surgical staging system for endometrial cancer to stage uterine sarcomas (see Table 33-8).

Table 34-3 FIGO Staging of Uterine Sarcomas

Stage	Description
I	Sarcoma is confined to the corpus.
II	Sarcoma has involved both the corpus and the cervix.
III	Sarcoma has extended outside the uterus but not outside the true pelvis.
IV	Sarcoma has extended outside the true pelvis or has involved the mucosa of the bladder or rectum

FIGO = International Federation of Gynecology and Obstetrics.

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TREATMENT OF EARLY-STAGE DISEASE

Surgery

The highest chance of cure is achieved by complete surgical resection of a tumor that is confined to the uterus. In general, an abdominal procedure is performed because of the typical features of sarcomas, which include uterine enlargement, parametrial extension, and tumor metastasis. For the most part, these patients are not suitable candidates for laparoscopic or vaginal surgery.

The staging laparotomy described for endometrial cancer can be revised in several ways to incorporate the unique spread patterns

of uterine sarcoma (see Chap. 33, Staging Laparotomy). For instance, peritoneal washings may be obtained easily on opening the abdomen but have limited value. Exploration is particularly important to assess the abdomen for unresectable or widely metastatic disease that might indicate a need to abort the procedure. Unlike endometrial carcinomas, there is no benefit to aggressive cytoreductive surgery.

With uterine leiomyosarcoma, all patients should undergo a hysterectomy, if feasible. A modified radical or radical procedure may be required occasionally if there is parametrial infiltration. In the absence of other gross disease, fewer than 5 percent of patients will have ovarian or nodal metastases. Ovarian preservation is therefore an option for premenopausal women. In addition, lymph node dissection should be reserved for patients with clinically suspicious nodes (Leitao, 2003; Major, 1993). For STUMP, hysterectomy alone is sufficient.

Endometrial stromal tumors and adenosarcomas also are best treated by hysterectomy. Again, a more radical procedure may be required to encompass local disease. Preservation of the ovaries generally is accepted for endometrial stromal sarcomas or adenosarcomas in the absence of extrauterine disease (Li, 2005). However, bilateral salpingo-oophorectomy (BSO) is indicated for high-grade undifferentiated sarcomas (Leibsohn, 1990). As with leiomyosarcoma, sampling of suspicious nodes is sufficient because detection of subclinical nodal disease has minimal impact on clinical management. Specifically, nodal metastases typically are identified only in patients with obvious extrauterine disease and portend rapid disease progression (Goff, 1993).

For uterine MMMT, hysterectomy and BSO are mandatory. Lymph node metastases develop in 15 to 20 percent of patients with clinical stage I disease, and thus retroperitoneal nodes should be sampled as for poorly differentiated endometrial cancers (Major, 1993). Typically, disease spread is consistent histologically with the carcinomatous element of this mixed tumor. Because this component may be serous or clear cell, extended surgical staging with infracolic omentectomy and random peritoneal biopsies is also advisable.

Surveillance

In women with surgical stage I uterine sarcoma, no adjuvant treatment has been demonstrated to improve survival. However, because the recurrence rate for the clinically aggressive types is excessive, enrollment in an experimental clinical trial should be considered carefully, if available. In practice, many patients receive postoperative radiation with or without chemotherapy, although data to support these treatments are limited. The remainder is simply monitored without further treatment. Women with endometrial stromal sarcoma should not receive estrogen-replacement therapy because of exquisite hormonal sensitivity of these tumors and the potential for disease progression (Chu, 2003; Pink, 2006).

Surgically treated stage I patients should have a physical examination every 3 months for the first 2 years and then at 6- to 12-month intervals thereafter. Most recurrences will be distant, and thus Pap tests are largely irrevelant. In addition, serum CA125 levels are not usually helpful. Depending on the sarcoma type, a chest radiograph should be performed every 3 to 6 months for 2 years and then annually. In many cases, intermittent CT scanning or MR imaging also may be indicated (Greer, 2006).

Adjuvant Radiation or Chemotherapy

The role of postoperative radiotherapy for nonmetastatic disease is controversial because most available data are retrospective. Prior retrospective studies of adjuvant radiotherapy have demonstrated a reduction in pelvic recurrence for MMMTs, leiomyosarcoma, and endometrial stromal sarcoma (Callister, 2004; Hornback, 1986). However, preliminary results from a prospective trial that randomly assigned women with surgical stage I or II uterine sarcomas to receive either pelvic radiation or no further treatment were reported recently. Although a reduction in pelvic relapse for those with MMMTs was noted, there was no benefit for those with leiomyosarcomas or endometrial stromal sarcomas (Reed, 2003). Whether these results will shape future treatment awaits final maturation of these early data.

In summary, most clinicians agree that enough evidence still supports use of pelvic radiation or brachytherapy with or without chemotherapy for surgical stage I and II leiomyosarcomas, MMMTs, and high-grade undifferentiated sarcomas (Greer, 2006; Le Pechoux, 2006).

Pelvic radiation, however, does not prevent distant recurrences. Accordingly, whole abdominal radiotherapy has been investigated to treat those with stage Iâ€"IV uterine MMMT. Study results are pending, but preliminary data do not suggest a benefit for whole

abdominal radiotherapy. Similarly, chemotherapy appears to be an ineffective adjuvant for most early-stage uterine sarcomas, and there is no proven role for chemotherapy in stage I disease following complete surgical resection.

Fertility-Sparing Management

Rarely, young patients may desire and meet criteria for fertility-sparing surgery. Although conservative management following tumor resection can result in successful pregnancies in selected patients, it is risky not to perform a hysterectomy for uterine sarcoma in most patients, even if margins are thought to be negative (Lissoni, 1998). Instead, if ovaries are left in situ during surgery for clinical stage I uterine leiomyosarcomas or endometrial stromal sarcomas, then egg retrieval and assisted reproductive technologies still would be possible (see Chap. 20, Assisted Reproductive Technologies). For more advanced disease, fertility-sparing management is not a reasonable option.

TREATMENT OF ADVANCED/RECURRENT DISEASE

Patients with advanced or recurrent uterine sarcoma generally have a dismal prognosis. In some circumstances, surgical resection may be feasibleâ€"for example, exenteration for an isolated relapse of leiomyosarcoma that develops following a long disease-free interval (Wydra, 2006). Palliative radiation also may have a role depending on the site and distribution of the tumor. In general, uterine sarcomas have a propensity for relapse at distant sites, and chemotherapy is required. However, current treatment options have modest efficacy, and patients should be encouraged to enroll in experimental clinical trials.

Leiomyosarcoma

Historically, doxorubicin was considered the most active single agent (Omura, 1983). However, treatment with ifosfamide or the combination of gemcitabine and docetaxel also has lead to clinical responses (see Chap. 27, Chemotherapeutic Drugs). (Bay, 2006; Hensley, 2002; Sutton, 1992).

For late recurrences of leiomyosarcoma, surgery must be individualized. Five-year survival rates of 30 to 50 percent have been reported following pulmonary resection for lung metastases. Local and regional recurrences also may be amenable to surgical resection.

Endometrial Stromal Tumors

Surgical resection may be feasible for some patients with recurrent endometrial stromal sarcoma, but hormone therapy is known to be particularly useful. In general, these tumors are estrogen- and progesterone-receptor (ER/PR) positive (Sutton, 1986). Progestins such as megestrol acetate and medroxyprogesterone acetate are used most commonly either postoperatively for advanced-stage disease or for relapses (Reich, 2006). Using this strategy, complete responses are often possible. Aromatase inhibitors and gonadotropin-releasing hormone (GnRH) agonists also have demonstrated activity (Burke, 2004; Leunen, 2004).

High-grade undifferentiated sarcomas do not exhibit the same level of sensitivity to hormonal agents primarily because they are usually ER/PR negative. Advanced disease or recurrences of these extremely rare tumors also typically are not amenable to surgical resection, although palliative radiation may have some utility. Systemic chemotherapy is usually the only option, and ifosfamide is currently being investigated (Mansi, 1990; Sutton, 1996).

Malignant Mixed MÃ¼llerian Tumor (MMMT)

The combination of ifosfamide and paclitaxel is the current treatment of choice for advanced or recurrent uterine MMMT. In a recent phase III GOG trial randomizing 179 patients, this regimen demonstrated a superior response rate (45 versus 29 percent) and survival advantage compared with ifosfamide alone (protocol 161) (Homesley, 2007). However, in general, effective palliative chemotherapeutic options for uterine MMMT are limited.

SURVIVAL AND PROGNOSTIC FACTORS

In general, women with uterine sarcoma have a poor prognosis (Table 34-4). In a study of 141 women followed for a median of 3 years, 74 percent died of disease progression. Of prognostic factors, FIGO stage is the most important overriding variable (Livi, 2003).

Table 34-4 Overall Survival of Uterine Sarcomas (All Stages)

Type	5-Year Survival
Malignant mixed mÃ¼llerian tumor	35%
Leiomyosarcoma	25%
Endometrial stromal tumors	
Endometrial stromal sarcoma	60%
High-grade undifferentiated sarcoma	25%

Compiled from Acharya, 2005, with permission.

Tumor histology is the other main predictor of clinical outcome. Leiomyosarcomas have the worst prognosis and are followed by MMMT and high-grade undifferentiated sarcomas (Livi, 2003). Endometrial stromal sarcomas and uterine adenosarcomas without sarcomatous overgrowth are the two notable exceptions. Patients with these tumors tend to have a good prognosis with an indolent growth pattern (Pautier, 2000; Verschraegen, 1998).

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EPITHELIAL OVARIAN CANCER: INTRODUCTION

In the United States, ovarian cancer accounts for more deaths than all other gynecologic malignancies combined. Worldwide each year, 204,000 women are diagnosed, and 125,000 women die from this disease (Sankaranarayanan, 2006). Of these, epithelial ovarian carcinomas comprise 90 to 95 percent of all cases, including the more indolent low-malignant-potential (borderline) tumors (Quirk, 2005). Because of the similarities of primary peritoneal carcinomas and fallopian tube cancers, they are included within this section for simplicity. In general, there is no effective screening test for ovarian cancer and few notable early symptoms. As a result, three quarters of patients have advanced disease when they are diagnosed. Aggressive debulking surgery, followed by platinum-based chemotherapy, usually results in clinical remission. However, up to 80 percent of women will develop a relapse that eventually leads to disease progression and death.

EPIDEMIOLOGY AND RISK FACTORS

One in 78 American women (1.3 percent) will develop ovarian cancer during her lifetime. Because the incidence has been declining slowly since the early 1990s, ovarian cancer has dropped to the eighth leading cause of cancer in women. In 2007, 22,430 new cases are estimated to develop in the United States. However, few patients are diagnosed early and subsequently cured. As a result, 15,280 deaths are expected, and ovarian cancer remains the fifth leading cause of cancer-related death (Jemal, 2007). Overall, the average age at diagnosis is in the early 60s.

Numerous reproductive, environmental, and genetic risk factors have been associated with the development of ovarian cancer (Table 35-1). The most important is a *family history* of breast or ovarian cancer, and approximately 5 to 10 percent of patients have an inherited genetic predisposition. For the other 90 to 95 percent with no identifiable genetic link for their ovarian cancer, most risk factors are related to a pattern of uninterrupted ovulatory cycles during the reproductive years. Repeated stimulation of the ovarian surface epithelium is hypothesized to lead to malignant transformation.

Table 35-1 Risk Factors for Developing Epithelial Ovarian Cancer
Nulliparity
Early menarche
Late menopause
White race
Increasing age
Residence in North America and northern Europe
Family history

Nulliparity is associated with long periods of repetitive ovulation, and women without children have double the risk of developing ovarian cancer (Purdie, 2003). Those with a history of infertility have an even higher risk. Although the reasons are unclear, it is more likely to be an inherent ovarian predisposition than an iatrogenic effect of ovulation-inducing drugs. For example, women

treated for infertility who achieve a live birth do not have an increased risk of ovarian cancer (Rossing, 2004). In general, risks decrease with each live birth, eventually plateauing in women delivering five times (Hinkula, 2006). One interesting theory to explain this protective effect is that pregnancy may induce shedding of premalignant ovarian cells (Rostgaard, 2003).

Early menarche and late menopause also have been associated with an increased risk of ovarian cancer. In contrast, breast feeding has a protective effect, perhaps by prolonging amenorrhea (Yen, 2003). Presumably by also preventing ovulation, long-term combination oral contraceptive use reduces the risk of ovarian cancer by 50 percent. The duration of protection lasts up to 25 years after the last use (Riman, 2002). In contrast, estrogen-replacement therapy after the menopause has an elevated risk (Lacey, 2006).

White women have the highest incidence of ovarian cancer among all racial and ethnic groups (Quirk, 2005). Compared with that of black and Hispanic women, the risk is elevated by 30 to 40 percent (Goodman, 2003). Although exact reasons are unknown, racial discrepancies in parity and rates of gynecologic surgery may account for some of the differences.

Tubal ligation and *hysterectomy* each have been associated with a substantial reduction in the risk of developing ovarian cancer (Hankinson, 1993). It has been postulated that any type of gynecologic procedure that precludes irritants from reaching the ovaries via ascension from the lower genital tract plausibly might exert a similar protective effect. For example, women who regularly use perineal talc have an elevated risk (Ness, 2000).

The overall incidence of ovarian cancer rises with *increasing age* up to the mid-70s before declining slightly among women beyond 80 years (Goodman, 2003). In general, aging allows an extended time to accumulate random genetic alterations within the ovarian surface epithelium.

Women *residing in North America, northern Europe,* or *any industrialized Western country,* for example, Israel, have a higher risk of ovarian cancer. Globally, the incidence varies greatly, but developing countries and Japan have the lowest rates. Regional dietary habits may be partly responsible (Kiani, 2006). For example, consumption of foods low in fat but high in fiber, carotene, and vitamins appears protective (Zhang, 2004).

A *family history* of ovarian cancer in a first-degree relative, that is, a mother, daughter, or sister, triples a woman's lifetime risk of developing ovarian cancer. The risks further escalate with two or more afflicted first-degree relatives. Identification of high-risk patients with family members having ovarian, breast, or colon cancer is currently the best prevention strategy (National Cancer Institute, 2007a). If a family history is comprised mainly of colon cancer, clinicians should be aware of the possibility of *hereditary nonpolyposis colorectal cancer* (HNPCC), also known as *Lynch syndrome.* Patients with this syndrome have a high lifetime risk of colon cancer (85 percent) and ovarian cancer (10 to 12 percent). Because the predominant gynecologic malignancy is endometrial cancer (40 to 60 percent lifetime risk), HNPCC is described in more detail in Chapter 33.

Hereditary Breast and Ovarian Cancer

GENETIC SCREENING

More than 90 percent of inherited ovarian cancers result from germline mutations in the *BRCA1* or *BRCA2* genes. Thus, any woman with two family members having ovarian or premenopausal (before age 50) breast cancer among their first- or second-degree relatives should be referred for genetic counseling (Frank, 1998).

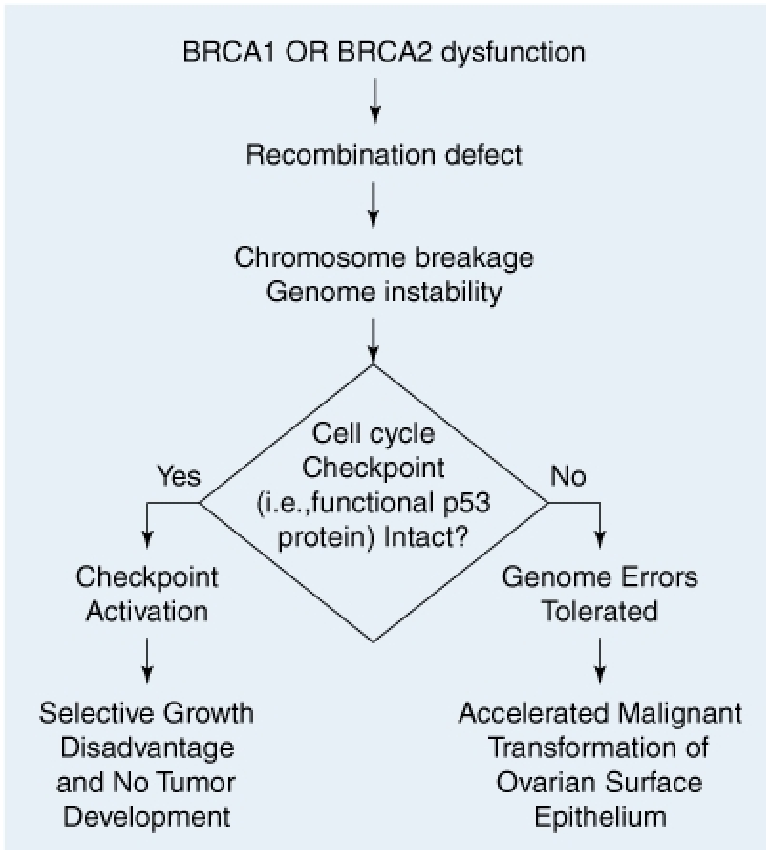
Typically, a comprehensive pedigree is constructed, and risk assessment is performed. BRCAPRO is currently the only validated statistical model for assessing an individual's risk for carrying a germline deleterious mutation of the *BRCA1* and *BRCA2* genes. This model and its associated software allow accurate quantification of this risk, and its results determine whether a patient should undergo genetic testing (Euhus, 2002; James, 2006).

BRCA1 AND *BRCA2* GENES

These are two tumor suppressor genes whose protein products, BRCA1 and BRCA2, interact with recombination/DNA-repair proteins to preserve intact chromosome structure. Mutations of *BRCA1* and *BRCA2* lead to genetic instability, subjecting cells to a higher risk of malignant transformation (Fig 35-1) (Deng, 2006; Scully, 2000). The *BRCA1* gene is located on chromosome 17q21. Patients with a proven mutation have a dramatically elevated risk of developing both breast (45 to 85 percent) and ovarian (20 to

45 percent) cancer. *BRCA2* is located on chromosome 13q12 and, in general, is less likely to lead to breast (30 to 50 percent) and ovarian (10 to 20 percent) cancer (Chen, 2006; Risch, 2006). Both genes are inherited in an autosomal dominant fashion, with variable penetrance. In essence, a carrier has a 50:50 chance of passing the gene to a son or daughter, but it is uncertain whether anyone with the gene mutation actually will develop breast or ovarian cancer. As a result, manifestations of *BRCA1* and *BRCA2* mutations can appear to skip generations.

FIGURE 35-1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Diagram describing the affects of the *BRCA* mutation leading to tumor development. Cells with damaged DNA are frequently blocked at checkpoints along the cell cycle and thereby prohibited from moving to the mitotic phase. *(Modified from Scully, 2000, with permission.)*

GENETIC TESTING

The main purpose of genetic testing is to identify women with deleterious *BRCA1* and *BRCA2* mutations, to intervene with prophylactic surgery, and thereby to prevent ovarian cancer. Three distinct results are possible with this testing. The first is identifying a recognized BRCA mutation. A positive test suggests the presence of a deleterious mutation. The most common are the three "Jewish founder" mutations: 185delAG or 5382insC in *BRCA1* and 6174delT in *BRCA2* . Each of these frameshift mutations significantly alters the downstream amino acid sequence, resulting in alteration of the BRCA1 or BRCA2 tumor suppressor protein.

As suggested, founder mutations are thought to have originated from within the Ashkenazi population thousands of years ago. As a result, Ashkenazi women with a single first-degree relative having either ovarian or premenopausal breast cancer also should be referred for genetic counseling.

Although Jewish founder mutations are most common, any frameshift mutation within the *BRCA* genes may result in a deleterious

predisposition to developing breast and ovarian cancer. These "variants of uncertain clinical significance" represent a second result of BRCA testing. These mutations actually may be pathogenic (true mutations) or may be just polymorphisms (normal variants found in at least 1 percent of alleles in the general population). These unclassified variants are common, representing about a third of *BRCA1* test results and half of those for *BRCA2* . Most are missense mutations, which result in a single-amino-acid change in the protein without a frameshift. Because of their uncertain clinical relevance, it is reasonable to ignore them and base patient counseling on family history (Gomez-Garcia, 2005).

Lastly, the third and most reassuring genetic test result is negative. However, because of the large size of the *BRCA1* and *BRCA2* genes, there is a false-negative rate of about 10 percent.

PREVENTION

Ovarian Cancer Screening

In addition to genetic testing, other screening strategies for ovarian cancer have been evaluated. However, despite enormous effort, there is no proof that routine screening with serum markers, sonography, or pelvic examinations decreases mortality. Hundreds of possible markers have been identified, yet no test currently available approaches sufficient levels of accuracy (American College of Obstetricians and Gynecologists, 2002).

HIGH-RISK WOMEN

For the most part, screening strategies are directed at *BRCA1* or *BRCA2* mutation carriers, in addition to women with a strong family history of breast and ovarian cancer. Most commonly, cancer antigen 125 (CA125) measurements and/or transvaginal sonography have been tested, albeit with marginal success. However, in *BRCA1* or *BRCA2* mutation carriers who do not wish to undergo prophylactic surgery, a combination of thorough pelvic examination, transvaginal sonographic evaluation, and CA125 blood testing should be offered.

By itself, CA125 is not a useful marker for detecting ovarian cancer. However, recently, a more sensitive *r* isk of *o* varian *c* ancer *a* lgorithm (ROCA) has been developed. This algorithm is based on the slope of serial CA125 measurements drawn at regular intervals (Kruitwagen, 1996; Skates, 2003). If a ROCA score exceeds a 1 percent risk of having ovarian cancer, patients undergo transvaginal sonography to determine whether additional intervention is warranted. This strategy is currently being studied prospectively among more than 2,000 high-risk women by the Gynecologic Oncology Group (GOG, protocol 199) and the National Cancer Instituteâ€"Cancer Genetics Network.

GENERAL POPULATION

Because no sufficiently accurate early detection tests are available currently, routine screening for women at average risk is not recommended. For example, in the U.S. prospective Prostate, Lung, Colorectal, and Ovarian (PLCO) Trial of screening versus usual care, 39,115 women were randomly assigned to CA125 and transvaginal sonography screening (Buys, 2005). Of those with an initially abnormal CA125 result and/or sonogram findings, 1 percent had invasive ovarian cancer, demonstrating a relatively low predictive value of both tests. To evaluate the efficacy, cost, morbidity, compliance, and acceptability of ROCA-based CA125 screening and study-directed sonography, a randomized trial of 200,000 asymptomatic postmenopausal women at average risk is currently underway [United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS)].

The nascent field of proteomics was shown initially to be a very promising new technology for the detection of early-stage ovarian cancer (Petricoin, 2002). By profiling the patterns of thousands of proteins with a high degree of sensitivity and specificity, it was hoped that an accurate test, such as OvaCheck (Correlogic Systems, Rockville, MD), would reliably distinguish those with early ovarian cancer from unaffected women. Unfortunately, neither proteomics nor any other screening strategy is currently near implementation into routine clinical practice.

Physical Examination

For the near future, the only recommendation for prevention of ovarian cancer in asymptomatic women is an annual pelvic examination. There are no additional techniques that have proved to be effective in routine screening (American College of Obstetricians and Gynecologists, 2002). In general, the pelvic examination can detect ovarian cancer only occasionally, generally

when the disease is already in advanced stages.

Chemoprevention

Oral contraceptive use is associated with a 50-percent decreased risk of developing ovarian cancer. However, there is a short-term increased risk of developing breast cancer that should be considered when counseling patients (National Cancer Institute, 2007c).

Prophylactic Surgery

The only proven way to prevent ovarian cancer is surgical oophorectomy. As another possible site of disease among high-risk patients, the fallopian tubes also should be removed (Levine, 2003). In *BRCA1* or *BRCA2* mutation carriers, prophylactic bilateral salpingo-oophorectomy (BSO) may be performed on either completion of childbearing or at age 35 (American College of Obstetricians and Gynecologists, 1999). In these patients, the procedure is approximately 90 percent effective in preventing epithelial ovarian cancer (Kauff, 2002; Rebbeck, 2002). In women with HNPCC, the risk reduction approaches 100 percent (Schmeler, 2006).

The term *prophylactic* implies that the ovaries are normal at the time of removal. However, about 5 percent of *BRCA* mutation carriers undergoing prophylactic BSO will have an otherwise undetected, often microscopic ovarian cancer at the time of surgery (Lu, 2000). To account for this possibility, cytologic washings, peritoneal biopsies, and an omental sample should be collected routinely during surgery. In addition, the ovaries and tubes should be sectioned serially to identify occult disease (Powell, 2005). Typically, the excision, washings, and biopsies all can be completed by minimally invasive laparoscopic surgery.

Prophylactic BSO in young women will induce premature menopause and its associated effects of vasomotor and urogenital symptoms, decline in sexual interest, and osteoporosis (National Cancer Institute, 2007c). Estrogen-replacement therapy is used commonly to alleviate these symptoms but may be less effective than is often assumed (Madalinska, 2006). Overall, mainly because the favorable impact on reducing cancer worries, prophylactic BSO does not adversely affect quality of life (Madalinska, 2005).

In addition to preventing ovarian cancer, prophylactic BSO reduces a woman's risk of developing breast cancer by 50 percent (Rebbeck, 2002). Predictably, the protective effect is strongest among premenopausal women (Kramer, 2005).

Hysterectomy is mandatory when performing prophylactic BSO in women with the HNPCC syndrome because of coexisting endometrial cancer risks. In *BRCA* mutation carriers, it is not required but should be part of the preoperative discussion. Theoretically, not removing the uterus leaves some residual adnexal tissue that potentially could give rise to "ovarian" cancer. In practice, this concern is unproven. Relatively few reports have suggested an association between *BRCA* mutations and an increased risk of endometrial cancer. Mainly, these develop in patients taking tamoxifen for breast cancer treatment or breast cancer chemopreventionâ€”which is another factor to consider during counseling regarding possible hysterectomy (Beiner, 2006). Obviously, hysterectomy may add to the potential morbidity and postoperative recovery time. In summary, some patients will wish to proceed with hysterectomy, whereas others prefer a more conservative approach.

LOW-MALIGNANT-POTENTIAL TUMORS

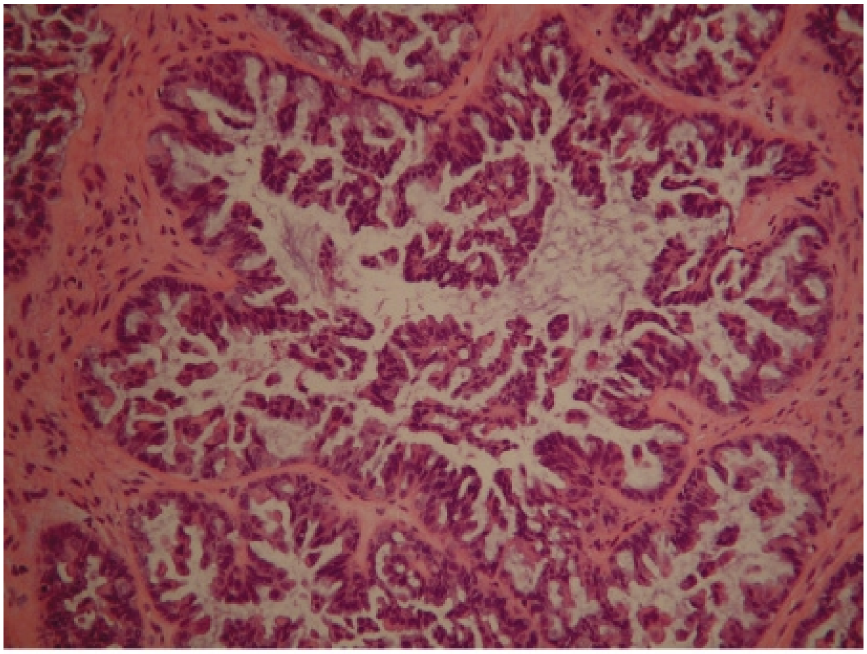
About 10 to 15 percent of epithelial ovarian cancers have histologic and biologic features that are intermediate between clearly benign cysts and frankly invasive carcinomas. In general, these low-malignant-potential (LMP), also termed *borderline* , tumors are associated with risk factors that are similar to epithelial ovarian cancer (Huusom, 2006). Typically, they are not considered to be part of any of the hereditary breast-ovarian cancer syndromes. Although LMP tumors may develop at any age, on average, patients are in their mid-40sâ€”some 15 years younger than women with invasive ovarian carcinoma. For a variety of reasons, their diagnosis and optimal management frequently are problematic.

Pathology

Histologically, LMP tumors are distinguished from benign cysts by having at least two of the following features: nuclear atypia, stratification of the epithelium, formation of microscopic papillary projections, cellular pleomorphism, and mitotic activity (Fig. 35-2). Unlike invasive carcinomas, LMP tumors are characterized by the *absence* of stromal invasion. However, up to 10 percent of LMP tumors will exhibit areas of microinvasion, defined as foci measuring less than 3 mm in diameter and comprising less than 5

percent of the tumor (Buttin, 2002). Due to the subtle nature of many of these findings, it is challenging to diagnose an LMP tumor with certainty based on frozen section.

FIGURE 35-2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photomicrograph of histologic specimen. Ovarian serous low malignant potential (LMP). *(Courtesy of Dr. Raheela Ashfaq.)*

Clinical Features

Ovarian LMP tumors present in the same manner as other adnexal masses. Women may have pelvic pain, distention, or increasing abdominal girth. Alternatively, an asymptomatic mass may be palpated during a routine pelvic examination. These tumors are detected occasionally as an incidental finding during routine obstetric sonographic examination or at the time of cesarean delivery.

As with other ovarian tumors, size varies widely from a serous tumor of less than 1 cm to a mucinous tumor that is larger than 30 cm, filling the entire abdomen. Preoperatively, there is no pathognomonic sonographic appearance, and serum CA125 measurements are nonspecific. Depending on the clinical setting, computed tomographic (CT) scanning may be indicated to exclude ascites or omental caking, which would suggest typical ovarian cancer. Regardless, any woman with a suspicious adnexal mass should have it removed (see Chap. 9, Human Chorionic Gonadotropin).

Treatment

Surgery is the cornerstone management for LMP tumors. The operative plan will vary depending on circumstances, and patients should be counseled carefully beforehand. All women should be prepared for the operating room with the intent to perform complete ovarian cancer surgical staging or debulking, if necessary (see Management of Early-Stage Ovarian Cancer). In many cases, a laparoscopic approach is appropriate. If laparotomy is planned, then a vertical incision is selected to allow access to the upper abdomen and para-aortic nodes, if needed, for cancer staging. Premenopausal women who have not completed childbearing may undergo fertility-sparing surgery with preservation of the uterus and contralateral ovary (Zanetta, 2001). This is a reasonable approach even if the final diagnosis shows invasive stage I cancer (Schilder, 2002). In contrast, postmenopausal women should undergo hysterectomy with BSO.

During surgery, peritoneal washings should be collected immediately on entering into the abdomen, followed by exploration. The

ovarian mass should be removed intact and submitted to pathology for frozen section evaluation. However, it is almost impossible to know with certainty whether a patient has a benign adnexal mass, LMP tumor, or invasive ovarian cancer until final histologic slides have been reviewed (Houck, 2000). In those with LMP diagnosed intraoperatively, limited staging biopsies of the peritoneum and omentum should be considered. Additionally, the appendix also should be examined and potentially removed, especially if the tumor has mucinous histology. In the absence of enlarged nodes or a frozen section suggestive of frankly invasive disease, routine pelvic and para-aortic lymph node dissection may not be necessary (Rao, 2004).

Low-malignant-potential tumors are staged in the same manner as invasive ovarian cancer (see Table 35-5). For the most part, surgical staging has limited value in altering the prognosis of those with LMP tumors unless invasive cancer is diagnosed ultimately (Wingo, 2006). Although 97 percent of gynecologic oncologists advocate comprehensive surgical staging of LMP tumors, in current practice it is performed in only 12 percent of patients (Lin, 1999; Menzin, 2000). Usually this occurs if the diagnosis is not suspected intraoperatively, and a clinician is alerted when the final pathology report has been completed. In this circumstance, consultation with a gynecologic oncologist is recommended, but comprehensive surgical restaging is not necessarily required if the tumor appears confined to a single ovary. However, if a cystectomy has been performed, the risk of residual disease should prompt removal of the entire adnexa with washings and limited staging (Poncelet, 2006).

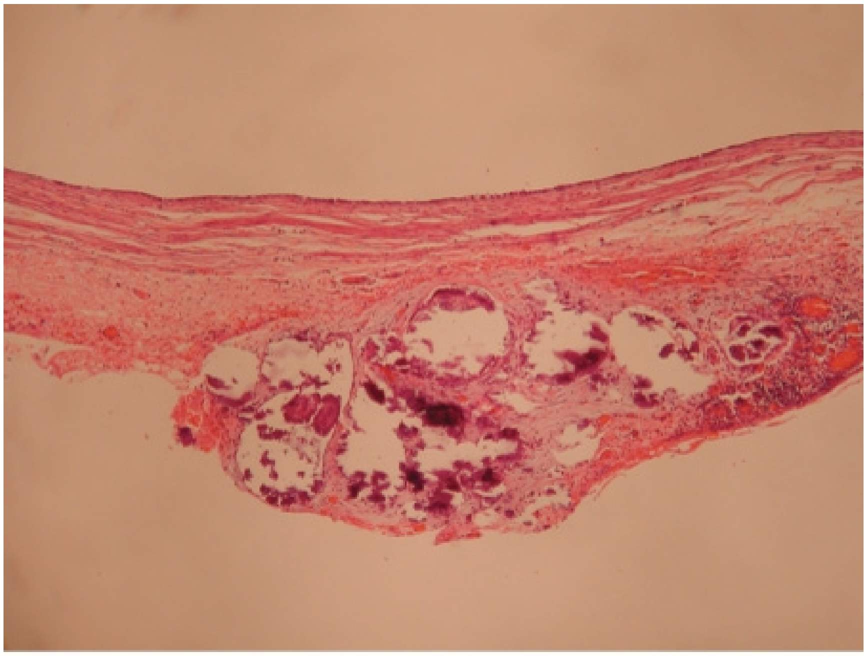
Table 35-5 FIGO Surgical Staging System for Ovarian Cancer

Stage	Surgical-Pathologic Findings
IA	Growth limited to one ovary
IB	Growth limited to both ovaries
IC	Tumor limited to one or both ovaries, but with disease on the surface of one or both ovaries; or with capsule(s) ruptured; or with malignant ascites or positive peritoneal washings
IIA	Extension and/or metastases to the uterus and/or tubes
IIB	Extension to other pelvic tissues
IIC	Tumor limited to the genital tract or other pelvic tissues, but with disease on the surface of one or both ovaries; or with capsule(s) ruptured; or with malignant ascites or positive peritoneal washings
IIIA	Tumor grossly limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal-peritoneal surfaces
IIIB	Abdominal implants less than 2 cm in diameter with negative nodes
IIIC	Abdominal implants at least 2 cm in diameter and/or positive pelvic, para-aortic, or inguinal nodes
IV	Distant metastases, including malignant pleural effusion or parenchymal liver metastases

FIGO = International Federation of Gynecology and Obstetrics. From Pecorelli, 1999, with permission.

For patients with stage IIâ€"IV disease, usually demonstrated by noninvasive implants (Fig. 35-3) or nodal metastases, the utility of adjuvant chemotherapy is speculative (Sutton, 1991). The most worrisome finding is the presence of invasive peritoneal implants. In general, these patients should be treated as if they have typical epithelial ovarian carcinoma, including de-bulking and postoperative chemotherapy.

FIGURE 35-3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photomicrograph of histologic specimen. Ovarian serous low malignant potential (LMP) in a peritoneal implant. *(Courtesy of Dr. Raheela Ashfaq.)*

Prognosis

The prognosis is excellent for patients with ovarian LMP tumors (Table 35-2). Overall, more than 80 percent have stage I disease, and if treated by hysterectomy and BSO, stage I tumors rarely, if ever, recur (Barnhill, 1995). Fertility-sparing surgery is associated with a 15-percent risk of relapse, usually in the contralateral ovary, but remains highly curable by reoperation and resection (Rao, 2005).

Table 35-2 Survival of Women with Ovarian Low-Malignant-Potential Tumors

Stage	5-Year Survival (%)
I	99
II	98
III	96
IV	77

From Trimble, 2002, with permission.

About 15 percent of LMP tumors are stage II and III disease, almost invariably of serous histology. Stage IV ovarian LMP tumors account for fewer than 5 percent of diagnoses and have the worst prognosis (Trimble, 2002). For advanced-stage tumors, the most reliable prognostic indicator is the presence of invasive peritoneal implants (Seidman, 2000).

Because of their indolent nature, symptomatic recurrence and death may develop as many as 20 years after therapy (Silva, 2006).

For most relapses, surgical excision is the most effective therapy. Chemotherapy typically is reserved for patients who develop ascites, have significant changes in the histologic features of the tumor, or demonstrate rapid tumor growth.

EPITHELIAL OVARIAN CANCER

Pathogenesis

There are at least three distinct tumorigenic pathways to account for the heterogeneity of epithelial ovarian cancer. First, relatively few cases seem to arise from an accumulation of genetic alterations leading to malignant transformation of benign cysts to LMP tumors and ultimately progressing to invasive ovarian carcinoma (Makarla, 2005). Typically, these invasive tumors are low grade and clinically indolent. In these tumors, K-*ras* oncogenic mutations occur early. The *ras* family of oncogenes includes K-*ras* , H-*ras* , and N-*ras* . Their protein products participate in cell cycle regulation and control of cell proliferation. As such, ras mutations have been implicated in carcinogenesis by their inhibition of cellular apoptosis and promotion of cellular proliferation (Mammas, 2005). In contrast, invasive cancers arising from LMP tumors have mutations in the *p53* tumor suppressor gene.

Second, about 5 to 10 percent of epithelial ovarian carcinomas result from an inherited predisposition. Women born with a *BRCA* mutation only require one "hit" to the other normal copy (allele) to "knock out" the *BRCA* tumor suppressor gene product. As a result, *BRCA* -related cancers develop about 15 years before sporadic cases. Thereafter, *BRCA* -related ovarian and peritoneal cancers appear to have a unique molecular pathogenesis, requiring *p53* inactivation to progress (Buller, 2001; Schorge, 2000). *p53* is a tumor suppressor gene that has been mapped to chromosome 17. Its protein product prohibits cells from entering subsequent stages of cell division and thereby halts uncontrolled tumor cell replication. Mutations in *p53* are linked with a variety of cancers. In fact, loss of *BRCA* and *p53* function has been detected prior to invasion, further supporting their importance as an early triggering event (Werness, 2000).

Third, the vast majority of carcinomas appear to originate de novo from ovarian surface epithelial cells that are sequestered in inclusion cysts within the ovarian stroma. Numerous inciting events and subsequent pathways have been proposed. For example, cyclic repair of the ovarian surface during long periods of repetitive ovulation requires abundant cellular proliferation. In these women, spontaneous *p53* mutations arising during the DNA synthesis that accompanies this proliferation appear to play a primary role in carcinogenesis (Schildkraut, 1997). Certainly, several developmental pathways are possible, stemming from early inactivation of innumerable genes.

Diagnosis

SIGNS AND SYMPTOMS

Ovarian cancer typically is portrayed as a "silent killer" without appreciable signs or symptoms until advanced disease is obvious clinically. This is a misconception. Actually, patients are often symptomatic for several months before the diagnosis, even with early-stage disease (Goff, 2000). The difficulty is in distinguishing these symptoms from those that occur normally in women.

In general, persistent symptoms that are more severe or frequent than expected and of recent onset warrant further diagnostic investigation. Women with malignant masses typically experience symptoms of notable severity 20 to 30 times per month. Commonly, increased abdominal size, bloating, urinary urgency, and pelvic pain are reported. Additionally, fatigue, indigestion, inability to eat normally, constipation, and back pain may be noted (Goff, 2004). Abnormal vaginal bleeding occurs rarely. Occasionally, patients may present with nausea, vomiting, and a partial bowel obstruction if carcinomatosis is particularly widespread. Unfortunately, many women and clinicians are quick to attribute such symptoms to menopause, aging, dietary changes, stress, depression, or functional bowel problems. As a result, weeks or months often pass before medical advice is sought or diagnostic studies are performed.

PHYSICAL EXAMINATION

A pelvic or pelvic-abdominal mass is palpable in most patients with ovarian cancer (Fig. 35-4). In general, malignant tumors tend to be solid, nodular, and fixed, but there are no pathognomonic findings that distinguish these growths from benign tumors. Paradoxically, a huge mass filling the pelvis and abdomen more often represents a benign tumor or low-grade malignancy. To aid surgical planning, a rectovaginal examination also should be performed. A woman with tumor impacted into the rectovaginal

septum may require a low anterior resection (see Section 43-19, Low Anterior Resection).

FIGURE 35-4

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photograph of a woman with a distended abdomen from a large ovarian mass.

The presence of a fluid wave or less commonly, flank bulging suggests the presence of significant ascites. In a woman with a pelvic mass and ascites, the diagnosis is ovarian cancer until proven otherwise. However, ascites without an identifiable pelvic mass suggests the possibility of cirrhosis or other primary malignancies such as gastric or pancreatic cancers. In advanced disease, examination of the upper abdomen usually reveals a central mass signifying omental caking.

Auscultation of the chest is also important because patients with malignant pleural effusions may not be overtly symptomatic. The remainder of the examination should include palpation of the peripheral nodes in addition to a general physical assessment.

LABORATORY TESTING

A routine complete blood count and metabolic panel often demonstrate a few characteristic features. For example, 20 to 25 percent of patients will present with thrombocytosis (platelet count > 400 $\times$ 10^9 /L) (Li, 2004). This is believed to result from malignant ovarian cells releasing cytokines that increase rates of platelet production. Hyponatremia, typically ranging between 125 and 130 mEq/L, is another common finding. In these patients, tumor secretion of a vasopressin-like substance can cause a clinical picture suggestive of a syndrome of inappropriate antidiuretic hormone (SIADH).

The serum CA125 test is integral to management of epithelial ovarian cancer. CA125 is a glycoprotein that is not produced by normal ovarian epithelium but may be produced by both benign and malignant ovarian tumors. This tumor marker is synthesized within affected ovarian epithelial cells and often secreted into cysts. In benign tumors, excess antigen is released into and may accumulate within cyst fluid. Hypothetically, abnormal tissue architecture associated with malignant tumors may allow antigen release into the vascular circulation (Verheijen, 1999).

In 90 percent of women presenting with malignant nonmucinous tumors, CA125 levels are elevated. However, preoperatively, it should not be used alone in the management of an adnexal mass (see Chap 9, Human Chorionic Gonadotropin). Half of stage I ovarian cancers will have a normal CA125 measurement (false negative). In contrast, an elevated value (false positive) may be

associated with a variety of common benign indications, such as pelvic inflammatory disease, endometriosis, leiomyomas, pregnancy, and even menstruation.

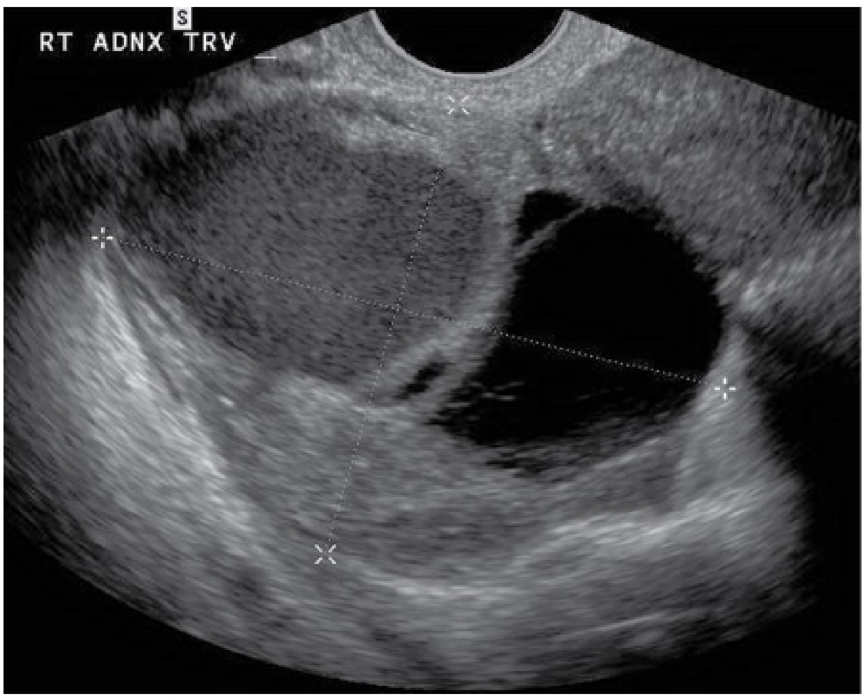
In postmenopausal women with a pelvic mass, a CA125 measurement may be helpful in predicting a higher likelihood of malignancy. This information is most useful when deciding whether to refer to a gynecologic oncologist (see Table 9-5). With mucinous tumors, the serum tumor markers cancer antigen 19-9 (CA-19-9) and carcinoembryonic antigen (CEA) may be better indicators of disease than CA125.

IMAGING

Sonography

To differentiate benign tumors and early-stage ovarian cancers, transvaginal sonography is typically the most useful imaging test (see Chap 2, Transvaginal Sonographic Endometrial Evaluation). In general, malignant tumors are multiloculated, solid or echogenic, large (>5 cm), and have thick septa with areas of nodularity (Figs. 35-5 and 35-6). Other features may include papillary projections or neovascularizationâ€”demonstrated by Doppler flow (Fig. 35-7). Although several presumptive models have been described in an attempt to distinguish benign masses from ovarian cancers preoperatively, none has been implemented universally (Timmerman, 2005; Twickler, 1999).

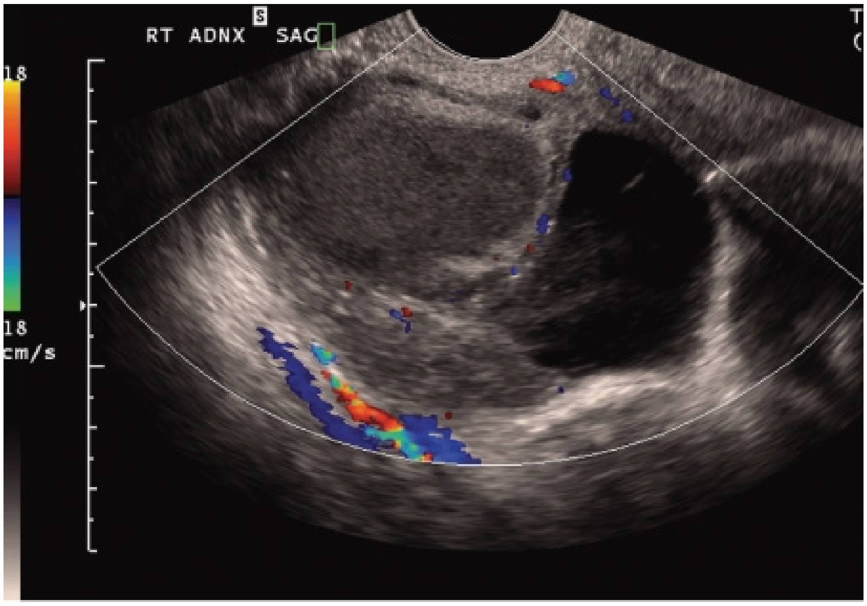
FIGURE 35-5



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Transvaginal sonogram depicts a complex ovarian mass. Cystic and solid components as well as a thick intracystic septum are seen. These findings increase clinical concern for malignancy. *(Courtesy of Dr. Diane Twickler.)*

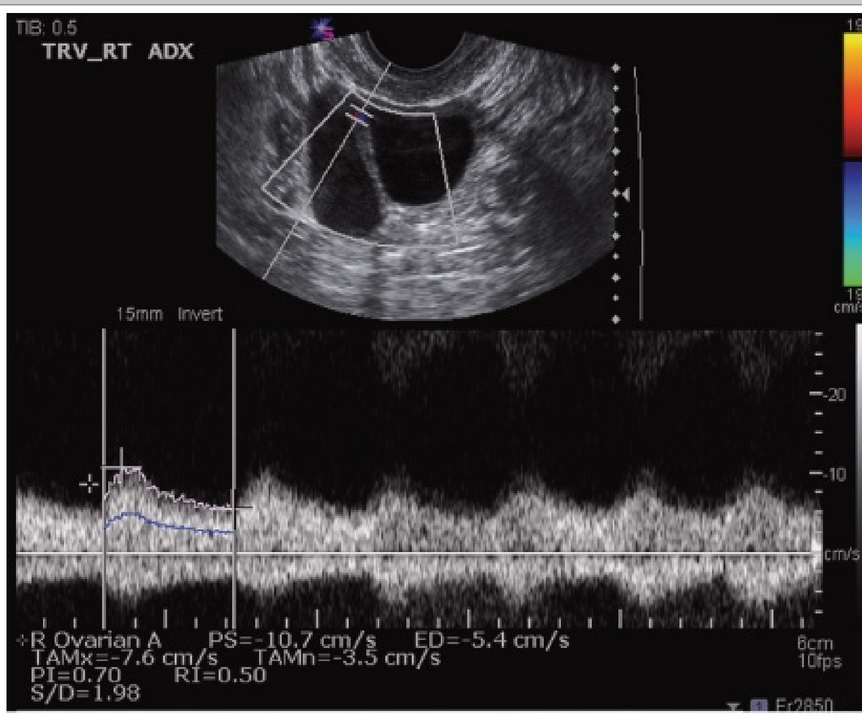
FIGURE 35-6



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Color Doppler transvaginal sonogram shows neovascularization within this ovarian tumor. *(Courtesy of Dr. Diane Twickler.)*

FIGURE 35-7



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Transvaginal Doppler study of ovarian mass vessels reveals decreased impedance. *(Courtesy of Dr. Diane Twickler.)*

In patients with advanced disease, sonography is less helpful. The pelvic sonogram may be particularly difficult to interpret when a large mass encompasses the uterus, adnexa, and surrounding structures. Ascites, if present, is easily detected, but abdominal sonography has limited use.

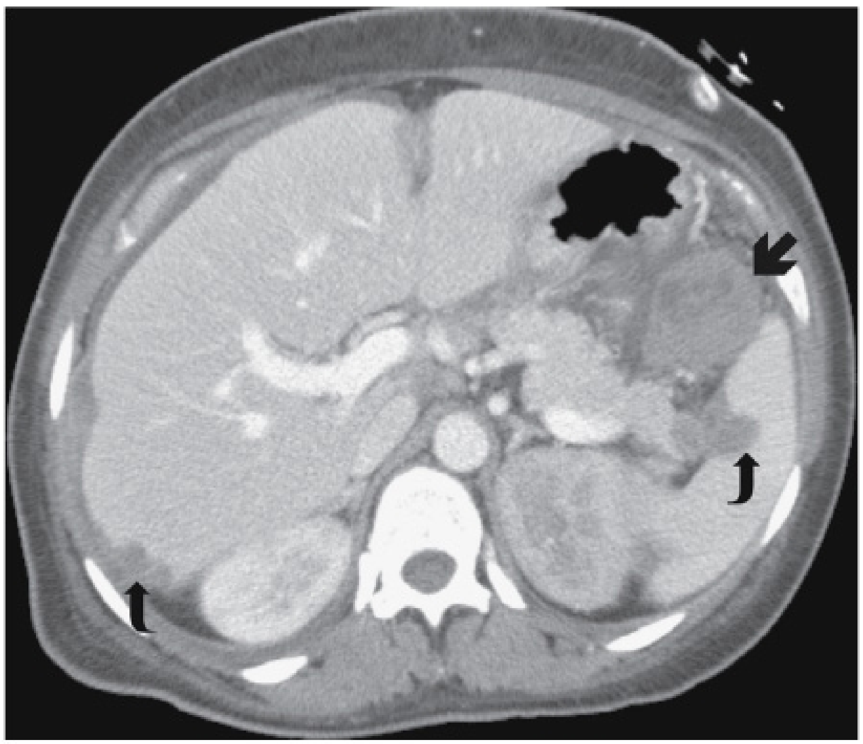
Radiography

Every patient with suspected ovarian cancer should have a chest radiograph to detect pulmonary effusions or infrequently, pulmonary metastases. Rarely, a barium enema is helpful clinically in excluding diverticular disease or colon cancer or in identifying involvement of the rectosigmoid by ovarian cancer.

Computed-Tomography Scanning

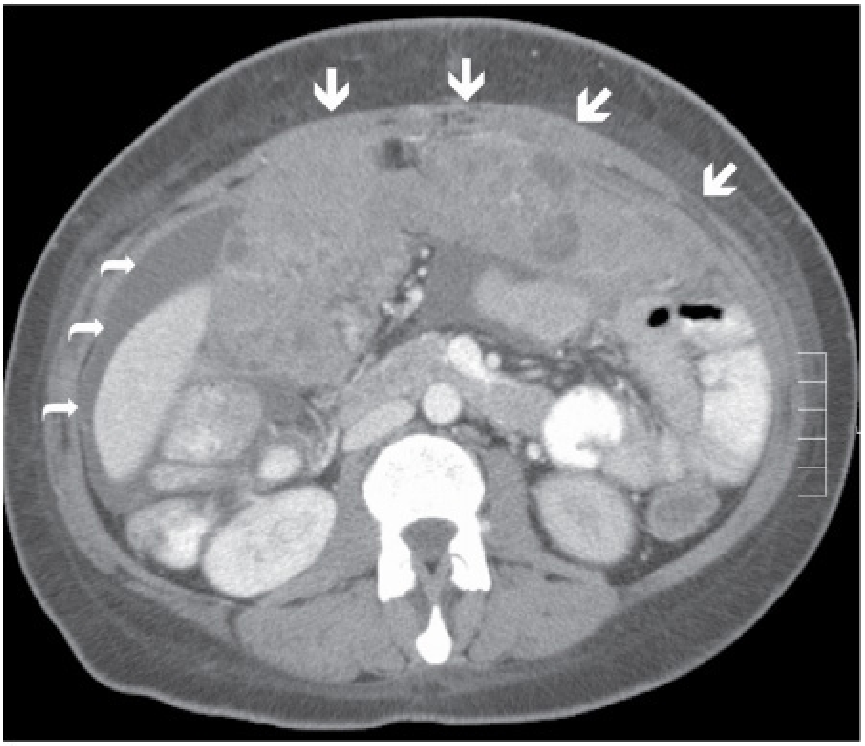
The main advantage of computed tomography (CT) scanning is in treatment planning of women with advanced ovarian cancer. Preoperatively, it may detect disease in the liver, retroperitoneum, omentum, or elsewhere in the abdomen and thereby guide surgical cytoreduction (Fig. 35-8). However, CT scanning is not particularly reliable in detecting intraperitoneal disease smaller than 1 to 2 cm in diameter. As a result, almost invariably, tumor sites not detected by CT scan are identified intraoperatively. Moreover, the accuracy of CT scanning is poor for differentiating a benign ovarian mass from a malignant tumor when disease is limited to the pelvis. In these cases, transvaginal sonography is superior.

FIGURE 35-8



A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Computed tomographic scans in a woman with ovarian cancer **A.** Axial CT scan at the level of the liver and spleen reveals metastatic lesions in the spleen and liver **(curved arrows)** and a bulky lesion at the splenorenal ligament **(arrow). B.** More caudal axial CT reveals ascites **(curved arrows)** and marked omental caking **(arrows)** . *(Courtesy of Dr. Diane Twickler.)*

In general, other radiologic studies such magnetic resonance (MR) imaging, bone scans, and positron-emission tomography (PET) typically provide little valuable information preoperatively.

PARACENTESIS

A woman with a pelvic mass and ascites can be assumed to have ovarian cancer until proven otherwise surgically. Thus few patients require a diagnostic paracentesis to guide treatment. Moreover, this procedure typically is avoided diagnostically because cytologic results usually are nonspecific, and abdominal wall metastases may form at the needle entry site (Kruitwagen, 1996). However, paracentesis may be indicated for patients with ascites and the *absence* of a pelvic mass.

Role of the Generalist

There is often tremendous difficulty in distinguishing benign from malignant disease using the currently available diagnostic modalities. However, the presence of ascites, evidence of abdominal or distant metastases, and a family history of one or more first-degree relatives with ovarian or breast cancer should prompt consideration of referral. Additionally, premenopausal women with very elevated CA125 levels (i.e., >200 units/mL) and postmenopausal women with any elevation are at higher risk for malignancy (American College of Obstetricians and Gynecologists, 2002).

Ideally, for women with suspicious adnexal masses, surgery should be performed in a hospital with a pathologist on staff. Surgeons should be prepared to appropriately stage and potentially debulk ovarian cancer or consult a gynecologic oncologist. At minimum, samples for peritoneal cytology should be obtained when the abdomen is entered. The mass then should be removed intact through an incision that permits thorough staging and resection of possible sites of metastasis (American College of Obstetricians and

Gynecologists, 2002). If the intraoperative frozen section suggests malignancy, then surgical staging should be performed. However, in a study of more than 10,000 women with ovarian cancer, almost half of those with early-stage disease did not undergo the recommended surgical procedures (Goff, 2006).

Ultimately, following treatment, many patients with early-stage disease will return to their referring physician at some point during postoperative surveillance. Monitoring for relapse is often coordinated between the gynecologic oncologist and generalist in obstetrics and gynecology, especially if no chemotherapy is required following surgery.

Pathology

Although epithelial ovarian cancer is often thought of as a single entity, the different histologic types (Table 35-3) are variable in their behavior. Commonly, two or more cell types are mixed. Within each histologic type, tumors are further categorized as benign, borderline (low malignant potential), or malignant.

Table 35-3 World Health Organization Histologic Classification of Ovarian Carcinoma
Serous adenocarcinoma
Mucinous tumors
Adenocarcinoma
Pseudomyxoma peritonei
Endometrioid Tumors
Adenocarcinoma
Malignant mixed mÃ¼llerian tumor
Clear cell adenocarcinoma
Transitional cell tumors
Malignant Brenner tumor
Transitional cell carcinoma
Squamous cell carcinoma
Mixed carcinoma
Undifferentiated carcinoma
Small cell carcinoma

From Tavassoli, 2003, with permission.

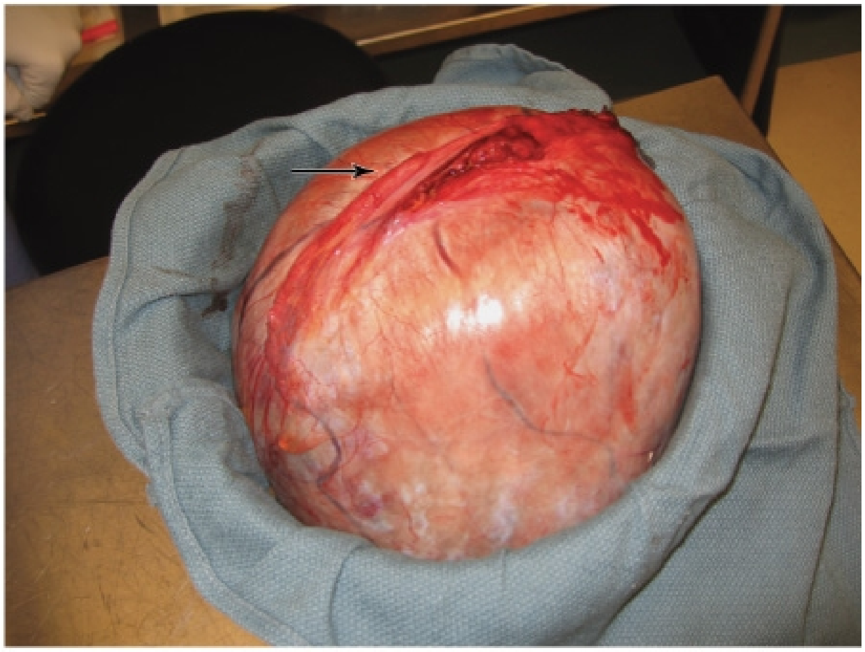
HISTOLOGIC GRADE

Mainly in early-stage disease, grade is an important prognostic factor that affects treatment planning (Morgan, 2006). Unfortunately, there is no universally accepted grading system for epithelial ovarian carcinoma. Instead, numerous different systems are used currently to assign grade. Most of these are based on architectural features and/or nuclear pleomorphism, with or without additional histopathologic criteria. In general, tumors are classified as grade 1 (well-differentiated), grade 2 (moderately differentiated), and grade 3 (poorly differentiated) lesions (Pecorelli, 1999).

HISTOLOGIC TYPE

Grossly, there are no distinguishing features among the types of epithelial ovarian cancer. In general, each has solid and cystic areas of varying sizes (Fig. 35-9).

FIGURE 35-9



A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

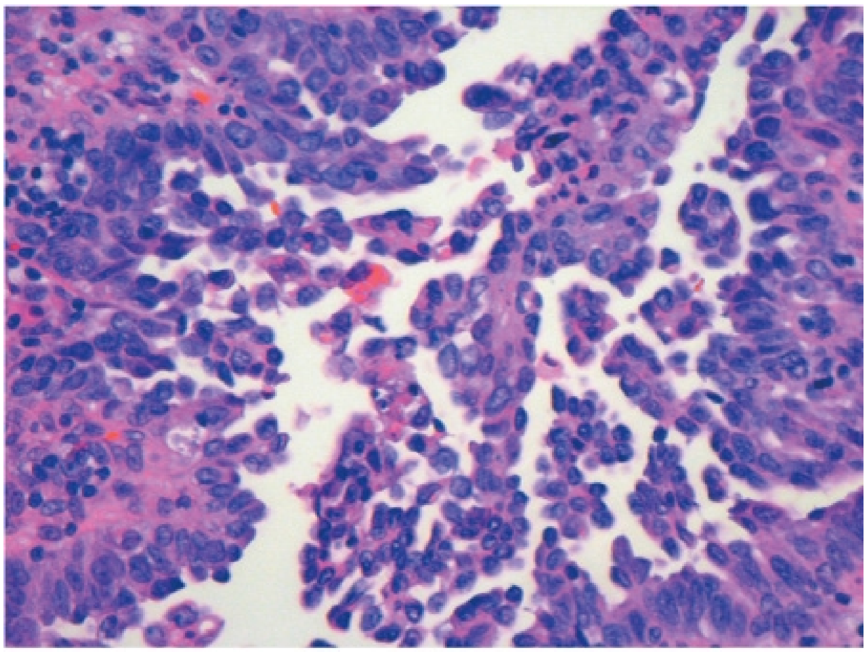
Gross photographs of an ovarian cystadenofibroma. **A.** Excised cystic ovarian mass. Note the fallopian tube stretched over the ovarian capsule **(arrow). B.** Opened tumor reveals the inner cyst wall and scattered papillary tumor growth **(arrow)** . *(Courtesy of Dr. David Miller.)*

SEROUS TUMORS

Adenocarcinoma

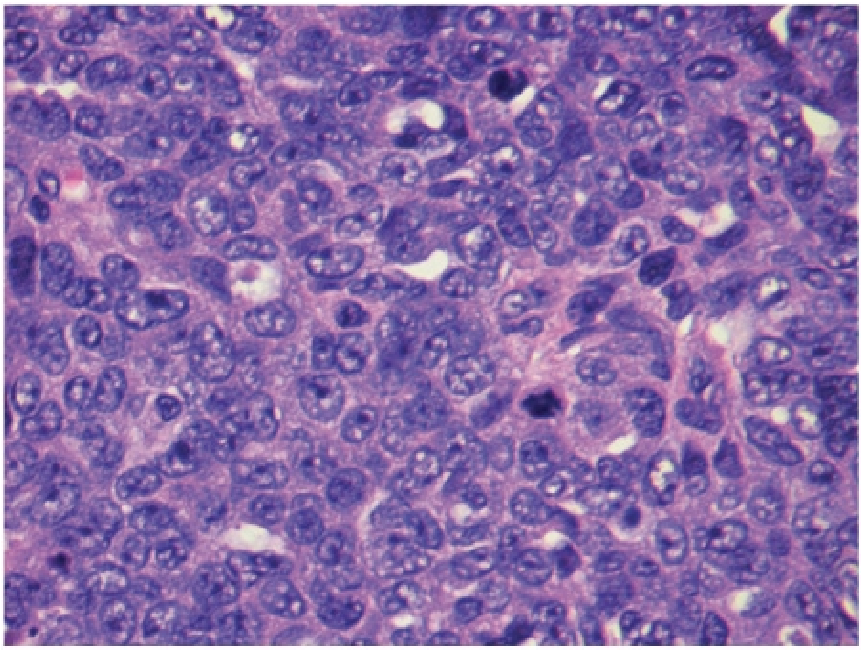
Half of all epithelial ovarian cancers have serous histology. Microscopically, the cells may resemble fallopian tube epithelium in well-differentiated tumors or anaplastic cells with severe nuclear atypia in poorly differentiated tumors (Fig 35-10). In well-differentiated tumors, the papillary structures are clearly formed within cystic areas, and psammoma bodies are identified frequently (Fig 35-11). During frozen section evaluation, psammoma bodies are essentially pathognomonic of an ovarian-type serous carcinoma. Often these tumors contain a variety of other cell types as a minor component (<10 percent) that may cause diagnostic problems but do not influence outcome (Lee, 2003).

FIGURE 35-10



A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

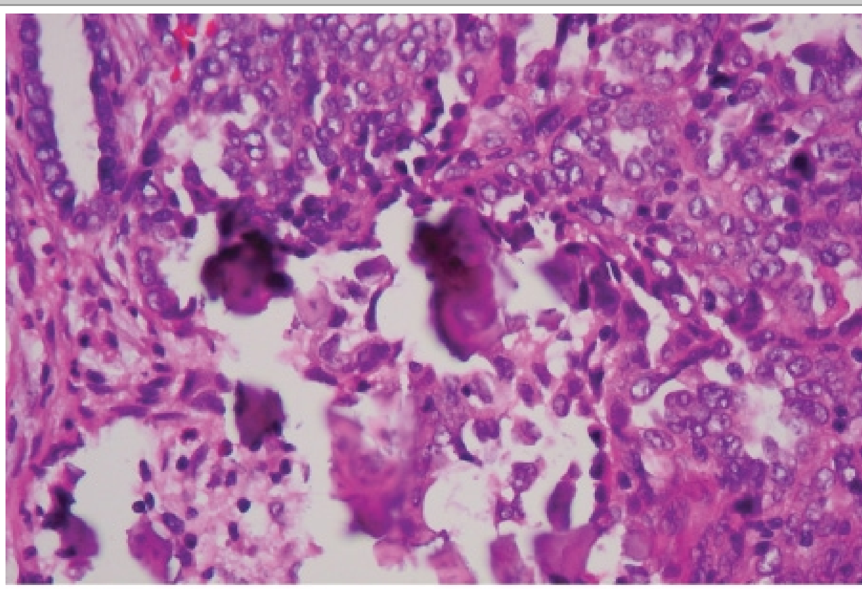


B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photomicrographs of histologic specimen of serous adenocarcinoma. **A.** Grade 1. **B.** Grade 3. *(Courtesy of Dr. Raheela Ashfaq.)*

FIGURE 35-11



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

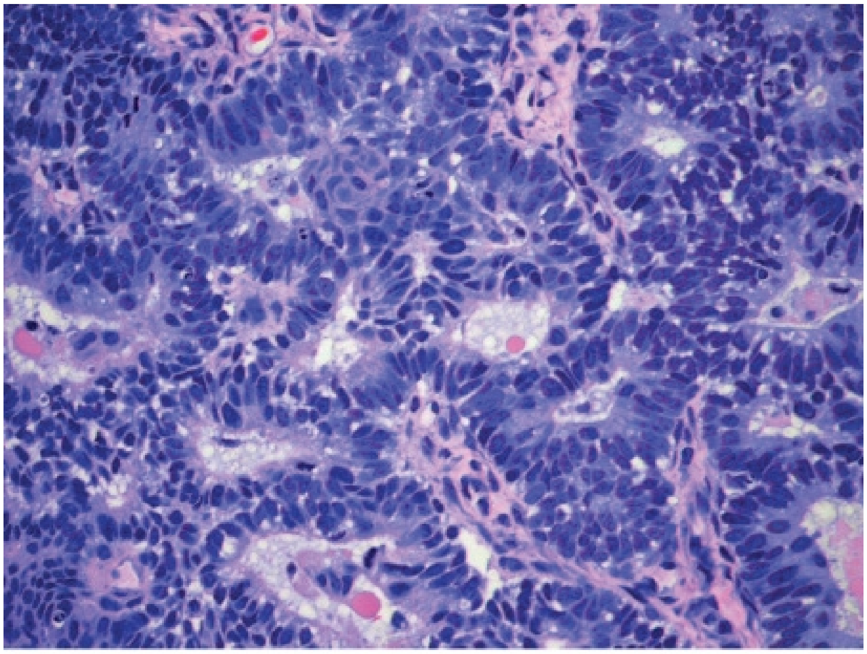
Photomicrograph of histologic specimen. Psammoma bodies. *(Courtesy of Dr. Raheela Ashfaq.)*

ENDOMETRIOID TUMORS

Adenocarcinoma

About 15 to 20 percent of epithelial ovarian cancers are endometrioid adenocarcinomas, the second most common histologic type (Fig. 35-12). However, the lower frequency results largely because poorly differentiated endometrioid and serous tumors cannot be distinguished easily, and such cases usually are classified as serous. As a result, well-differentiated endometrioid tumors are proportionally more common, which also may explain this tumor's overall relatively good prognosis.

FIGURE 35-12



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photomicrograph of histologic specimen of endometrioid adenocarcinoma. Microscopically, well-differentiated endometrioid variants closely resemble adenocarcinomas of the endometrium, often exhibiting many of the same features (i.e., squamous differentiation). Psammoma bodies are present occasionally. Poorly differentiated ovarian endometrioid adenocarcinomas have a mainly solid pattern. The presence of residual microglandular areas distinguishes these tumors from serous or undifferentiated histologic types. *(Courtesy of Dr. Raheela Ashfaq.)*

In 15 to 20 percent of cases, there is a coexisting endometrial adenocarcinoma. This is usually regarded as a synchronous tumor, but metastasis from one site to the other is difficult to exclude (Soliman, 2004). It has been hypothesized that a mÃ¼llerian "field effect" accounts for these independently occurring, histologically similar tumors. In addition, many such patients are noted to have pelvic endometriosis.

Malignant Mixed MÃ¼llerian Tumor

These rare tumors represent less than 1 percent of ovarian cancers and are histologically similar to uterine primary tumors. By definition, they contain malignant epithelial and mesenchymal elements.

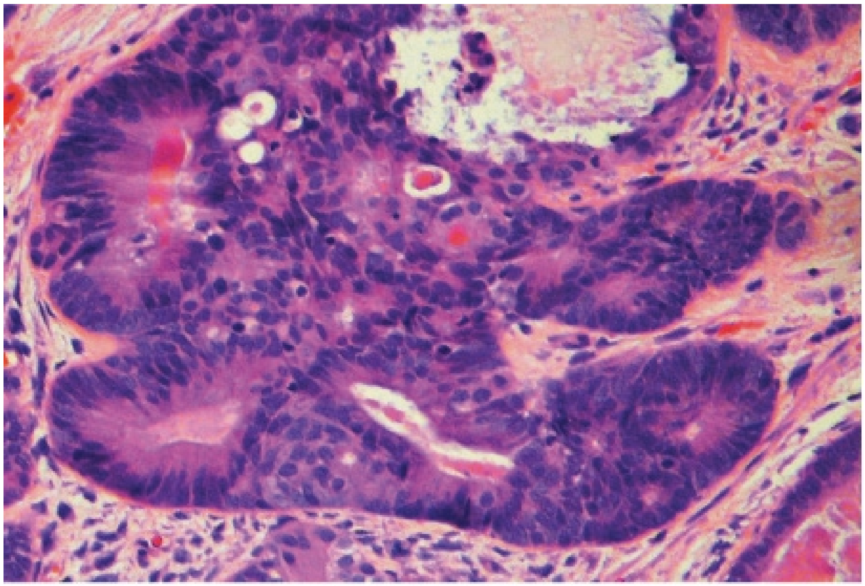
MUCINOUS TUMORS

Adenocarcinoma

About 5 to 10 percent of true epithelial ovarian cancers are mucinous adenocarcinomas. The frequency is usually overestimated because of undetected primary intestinal sites, such as the appendix or colon.Well-differentiated ovarian mucinous tumors closely resemble mucin-secreting adenocarcinomas of intestinal or endocervical origin (Fig. 35-13). Histologically, the distinction may be

impossible without clinical correlation (Lee, 2003).

FIGURE 35-13



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photomicrograph of histologic specimen of mucinous adenocarcinoma. *(Courtesy of Dr. Raheela Ashfaq.)*

Pseudomyxoma Peritonei

Pseudomyxoma peritonei is a clinical term used to describe the rare finding of abundant mucoid or gelatinous material in the pelvis and abdominal cavity surrounded by thin fibrous capsules. An ovarian mucinous carcinoma with ascites rarely results in this condition, and there is compelling evidence that ovarian mucinous tumors associated with pseudomyxoma peritonei are almost all metastatic rather than primary. As a result, appendiceal or other intestinal sites of origin should be excluded (Ronnett, 1997). The primary appendiceal tumor may be small relative to the ovarian tumor(s) and may not be appreciated macroscopically. Thus removal and thorough histologic examination of the appendix are indicated in all cases of pseudomyxoma peritonei.

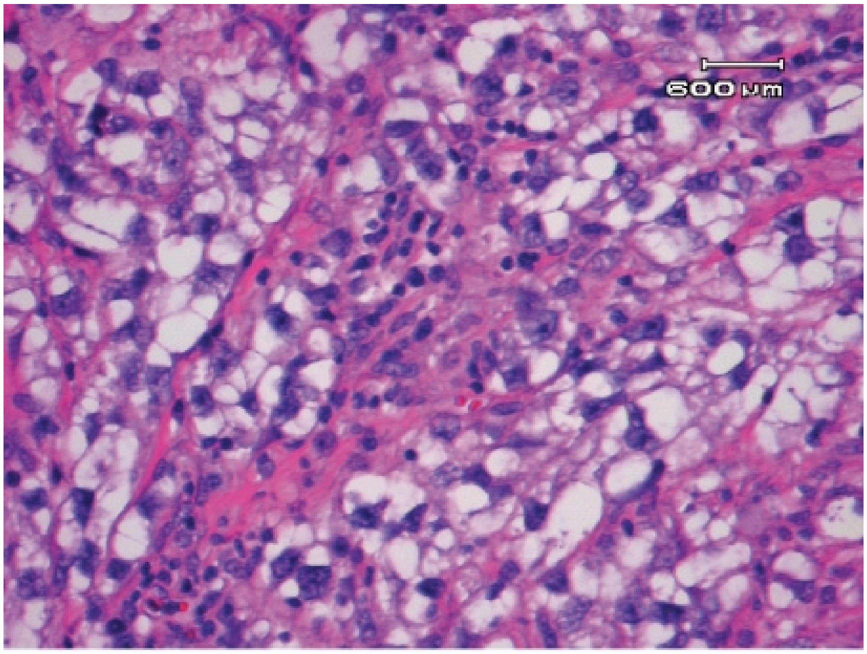
If the peritoneal epithelial cells are benign or borderline-appearing, the condition is referred to as *disseminated peritoneal adenomucinosis.* Patients with this diagnosis have a benign or protracted, indolent clinical course (Ronnett, 2001). When the peritoneal epithelial cells appear malignant, the clinical course is invariably fatal.

Clear Cell Adenocarcinoma

Comprising 5 to 10 percent of epithelial ovarian cancers, clear cell adenocarcinomas are the most frequently associated with pelvic endometriosis. The appearance of these tumors is similar to that of clear cell carcinomas that develop sporadically in the uterus, vagina, and cervix.

Microscopically, both clear and "hobnail" cells are characteristic (Fig. 35-14). In clear cells, the visibly clear cytoplasm results from the dissolution of glycogen as the tissue specimen is prepared histologically. Hobnail cells have bulbous nuclei that protrude far into the cystic lumen beyond the apparent cytoplasmic limits of the cell (Lee, 2003).

FIGURE 35-14



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photomicrograph of histologic specimen of clear cell adenocarcinoma. *(Courtesy of Dr. Raheela Ashfaq.)*

TRANSITIONAL CELL TUMORS

Malignant Brenner Tumor

These rare ovarian cancers are characterized by the coexistence of a poorly differentiated transitional cell carcinoma and interspersed foci of a benign or borderline Brenner tumor. Microscopically, the transitional cell component resembles carcinomas arising from the urinary tract, often having squamous differentiation. Brenner tumors are characterized by having a dense, unusually abundant, fibrous stroma with embedded nests of transitional epithelium.

Transitional Cell Carcinoma

Accounting for fewer than 5 percent of ovarian cancers, these tumors are characterized histologically by the absence of a demonstrable Brenner component. Patients with transitional cell carcinoma have a worse prognosis than those with malignant Brenner tumors but better than those with other histologic types of epithelial ovarian cancer (Gershenson, 1993). Microscopically, it resembles a primary bladder carcinoma but has an immunoreactive pattern consistent with ovarian origin (Lee, 2003).

Squamous Cell Carcinoma

Rarely, tumors may be classified as primary squamous cell carcinoma. In fact, this is the newest category to be recognized. More commonly, squamous cell carcinomas arise from mature cystic teratomas (dermoid cysts) and are classified as malignant ovarian germ cell tumors (see Chap. 36). In other cases, ovarian endometrioid variants may have extensive squamous differentiation, or alternatively, metastases from a cervical primary are present.

Mixed Carcinoma

When more than 10 percent of an ovarian cancer exhibits a second cell type, it is classified as a mixed tumor. Common combinations include mixed clear cellâ€"endometrioid or serous-endometrioid adenocarcinomas.

Undifferentiated Carcinoma

Rarely, epithelial ovarian tumors are too poorly differentiated to be classified into any of the mÃ¼llerian types described earlier. Microscopically, the cells are arranged in solid groups or sheets with numerous mitotic figures and marked cytologic atypia. Typically, there are foci of mÃ¼llerian carcinoma, usually serous, within the tumor. Overall, undifferentiated carcinomas of the ovary have a very poor prognosis compared with the other histologic types (Silva, 1991).

Small Cell Carcinoma

These tumors are rare, extremely malignant, and consist of two subgroups. Most patients have a *hypercalcemic type,* which typically develops in young women during their 20s. Nearly all these tumors are unilateral, and two thirds are associated with elevated serum calcium levels that resolve postoperatively (Young, 1994). The *pulmonary type* resembles oat cell carcinoma of the lung and develops in older women, and half of cases have bilateral ovarian disease (Eichhorn, 1992). In general, patients with small cell carcinoma die within 2 years from rapid disease progression.

Primary Peritoneal Carcinoma

Up to 15 percent of typical epithelial ovarian cancers are actually primary peritoneal carcinomas that arise de novo from the lining of the pelvis and abdomen. In some cases, especially among *BRCA1* mutation carriers, independent malignant transformation occurs at multiple peritoneal sites simultaneously (Schorge, 1998). Clinically and histologically, these tumors are virtually indistinguishable from epithelial ovarian cancer. However, primary peritoneal carcinoma may develop in a woman years after undergoing BSO. If ovaries are still present, several criteria are required to make the diagnosis (Table 35-4). By far the most common variant is papillary serous, but any of the other histologic types are possible. In general, the staging, treatment, and prognosis of primary peritoneal carcinoma are the same as for epithelial ovarian cancer (Mok, 2003). The differential diagnosis mainly includes malignant mesothelioma.

Table 35-4 Criteria for Diagnosing Primary Peritoneal Carcinoma When Ovaries Are Present

1. Both ovaries must be normal in size or enlarged by a benign process
2. The involvement in the extraovarian sites must be greater than the involvement on the surface of either ovary
3. The ovarian tumor involvement must be either non- existent, confined to the ovarian surface epithelium without stromal invasion, or involving the cortical stroma with tumor size less than 5 x 5 mm.

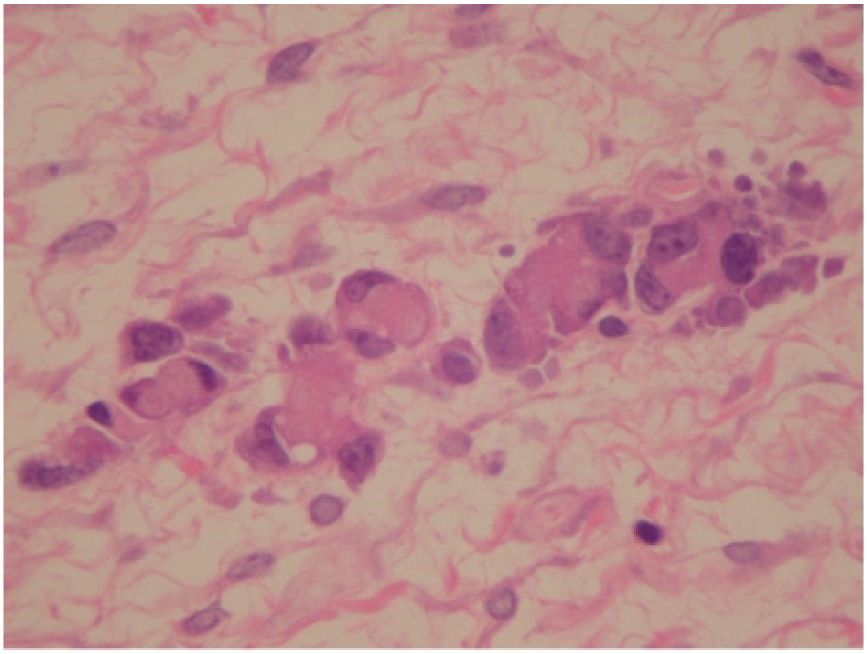
Fallopian Tube Carcinoma

Although much rarer than epithelial ovarian cancer, fallopian tube carcinomas otherwise have many clinical similarities. For the most part, risk factors, histologic types, surgical staging, pattern of spread, treatment, and prognosis are comparable. To be considered a primary carcinoma of the fallopian tube, the tumor must be located macroscopically within the tube or its fimbriated end. Additionally, the uterus and ovary must not contain carcinoma, or if they do, it must be clearly different from the fallopian tube lesion (Alvarado-Cabrero, 2003).

Secondary Tumors

Malignant tumors that metastasize to the ovary almost invariably are bilateral. The term *Krukenberg tumor* refers to a metastatic mucinousâ€"signet ring cell adenocarcinoma of the ovaries that typically originates from primary tumors of the intestinal tract, characteristically the stomach (Fig. 35-15). Ovarian metastases often represent a late disseminated stage of the disease in which other hematogenously disseminated metastases are also found (Prat, 2003).

FIGURE 35-15



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photomicrograph of histologic specimen of Krukenberg tumor. Signet-ring cells are seen as those with abundant pale cytoplasm and eccentric nuclei.*(Courtesy of Dr. Raheela Ashfaq.)*

PATTERNS OF SPREAD

In general, epithelial ovarian cancers metastasize predominantly by *exfoliation* . Malignant cells are first released into the peritoneal cavity when a tumor penetrates through the ovarian capsule surface. By following the normal circulation of peritoneal fluid, implants then may develop anywhere in the abdomen. A unique characteristic of ovarian cancer is that metastatic tumors usually do not infiltrate visceral organs but exist as surface implants. As a result, aggressive debulking is possible with reasonable morbidity.

Because of its marked vascularity, the omentum is the most frequent location for disease spread and is often involved extensively with tumor (Fig. 35-16). Nodules are also commonly present on the undersurface of the right hemidiaphragm and small bowel serosa, but all intraperitoneal surfaces are at risk.

FIGURE 35-16

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

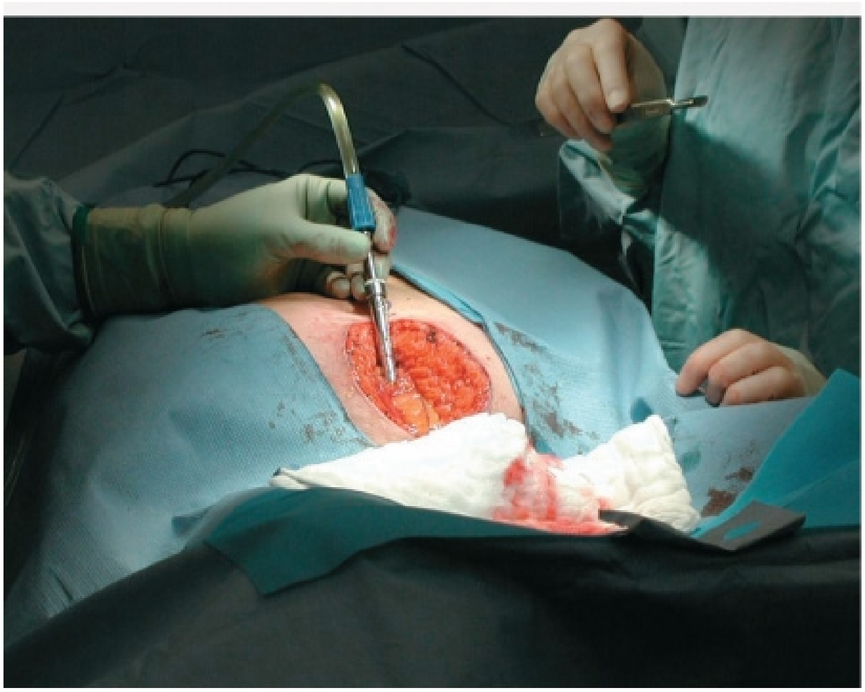
Photograph showing omental caking caused by tumor invasion.

Lymphatic dissemination is the other primary mode of spread. Malignant cells may spread via channels that follow the ovarian blood supply along the infundibulopelvic ligament, terminating in para-aortic lymph nodes up to the level of the renal vessels. Other lymphatics pass laterally through the broad ligament and parametrium to the external iliac, obturator, and internal iliac nodal chains (see Fig. 38-16). Infrequently, metastases also may follow the round ligament to the inguinal nodes (Lee, 2003).

Direct extension of a progressively enlarging ovarian cancer may result in confluent tumor involvement of the pelvic peritoneum and adjacent structures, including the uterus, rectosigmoid colon, and fallopian tubes. Usually, this is associated with significant induration of the surrounding tissues.

In advanced disease, several liters of ascites may be present (Fig. 35-17). Generally, this is believed to result from either increased production of carcinomatous fluid or decreased clearance by lymphatic channel obstruction. Similarly, by traversing the diaphragm, a malignant pleural effusion may develop.

FIGURE 35-17



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photograph showing intraoperative suction removal of several liters of ascitic fluid on entering the abdomen.

Hematogenous spread is atypical. In most cases, metastases to the liver or lung parenchyma, brain, or kidneys are observed in patients with recurrent disease, not at initial diagnosis.

STAGING

Ovarian cancer is staged surgically based on the typical patterns of spread (Table 35-5). Even if a tumor appears clinically to be confined to the ovary, in many cases it will have detectable metastases. Therefore, accurate surgical staging is crucial to guide treatment. About a third of patients have surgical stage I or II disease (Table 35-6).

Table 35-6 Distribution of Epithelial Ovarian Cancer by FIGO Stage (*n* = 4,825 Patients)

FIGO Stage	Percent
I	28
II	8
III	50
IV	13

FIGO = International Federation of Gynecology and Obstetrics. From Heintz, 2006, with permission.

Management of Early-Stage Ovarian Cancer

SURGICAL STAGING

When a malignancy appears clinically confined to the ovary, surgical removal and comprehensive staging should be performed. A third of patients who appear to have disease confined to the ovary will be "up-staged" by surgical staging and require postoperative chemotherapy. In those with stage IA or IB, grade 1 or 2 epithelial ovarian carcinoma, further treatment is unnecessary (Young, 1990).

Typically, the abdominal incision must be adequate to identify and resect any disease that may have been missed on physical examination or imaging tests. The operation begins by aspirating free ascitic fluid or collecting peritoneal washings, followed by visualization and palpation of all peritoneal surfaces. The infracolic omentum should be removed or at least biopsied (see Section 43-12, Omentectomy). Next, an extrafascial (simple) hysterectomy and BSO are performed (see Section 41-19, Hysterectomy). In the absence of gross extraovarian disease, peritoneal biopsies are obtained, along with a biopsy or scraping of the right diaphragm. Finally, a pelvic and infrarenal para-aortic lymphadenectomy is completed (see Sections 43-9, Pelvic Lymphadenectomy and 43-10, Para-Aortic Lymphadenectomy) (Whitney, 2005).

Laparoscopic staging is particularly valuable as a primary treatment in women who have an apparent stage I ovarian cancer. In those with unstaged disease, patients may have completion of their staging by laparoscopy. In general, all the required procedures can be performed safely with laparoscopy (Chi, 2005). The main putative benefits are a shorter hospital stay and quicker recovery (Tozzi, 2004). However, there is a learning curve for lymphadenectomy using this emerging, minimally invasive technique. Nodal counts may be inferior, and exploration of the abdomen is unavoidably limited. For a variety of reasons, including the presence of adhesions and/or unanticipated metastatic disease, up to 20 percent of laparoscopic cases will be converted to laparotomy (Spirtos, 2005).

FERTILITY-SPARING MANAGEMENT

Since about 10 percent of epithelial ovarian cancers develop in women younger than 40 years of age, fertility-sparing surgery may be an option in selected patients when disease appears confined to one ovary. Although many patients will be up-staged, those with surgical stage I disease have an excellent long-term survival with unilateral adnexectomy. In some cases, postoperative chemotherapy may be required, but patients usually will retain their ability to conceive and ultimately carry a pregnancy to term (Schilder, 2002).

ADJUVANT CHEMOTHERAPY

In general, patients with stage IA or IB, grade 3 epithelial ovarian cancer and all patients with stage IC and II tumors should be treated with three to six cycles of carboplatin (Paraplatin, Bristol-Myers Squibb, Princeton, NJ) and paclitaxel (Taxol, Bristol-Myers Squibb, Princeton, NJ) chemotherapy (Morgan, 2006; Trimbos, 2003). In a phase III GOG trial (protocol 157), women with early-stage disease were randomly assigned to either three or six cycles of this combination. Overall, three cycles resulted in a comparable relapse rate as six cycles but was associated with less toxicity (Bell, 2006).

Despite chemotherapy, more than 20 percent of women with early-stage disease develop recurrences within 5 years, suggesting the need for a better treatment strategy. In response, the GOG is currently performing a randomized phase III trial of three cycles of adjuvant carboplatin and paclitaxel chemotherapy followed by observation or weekly paclitaxel for 24 weeks (protocol 175).

SURVEILLANCE

After completion of treatment, patients with early-stage ovarian cancer may be followed every 2 to 4 months for the first 2 years, then twice yearly for an additional 3 years, and then annually. At each visit, complete physical and pelvic examinations should be performed. In addition, a serum CA125 determination is indicated if the level was elevated initially. If warranted clinically, imaging tests also may be helpful to exclude recurrent disease (Morgan, 2006).

Management of Advanced Ovarian Cancer

Approximately two thirds of patients will have stage IIIâ€“IV disease. Thus, multimodality therapy is particularly important to achieve the most successful outcome (Earle, 2006). Ideally, surgical cytoreduction is performed initially to remove all gross disease, that is, optimal tumor debulking. Surgery is followed by six courses of platinum-based chemotherapy. However, some women will not be appropriate candidates for primary surgery because of their medical condition, and others will have unresectable tumor. To balance all clinical factors effectively, each patient should be assessed individually before embarking on a treatment

strategy.

PRIMARY CYTOREDUCTIVE SURGERY

Residual Disease

Since the initial report by Griffiths in 1975 suggested the value of debulking, its value largely has been assumed. Numerous retrospective studies subsequently have supported the apparent survival advantage in women with advanced ovarian cancer if less than 2 cm of residual disease can be achieved by cytoreduction. Specifically, *2 cm of residual disease* describes a surgical result in which none of multiple remaining areas of tumor individually measures greater than 2 cm. Additional incremental improvements in survival have been demonstrated if residual disease is less than 1.5 cm, less than 1 cm, or less than 0.5 cm. Longest survival durations are reported if no residual disease remains at the surgery completion (Eisenkop, 1998). By definition, for patients to be considered "optimally debulked", that is, to display *minimal residual disease,* they must have areas of residual tumor that measure less than 1 cm.

There are several reasons why resecting ovarian cancer implants is believed to prolong survival. First, surgery removes large volumes of chemoresistant tumor cell clones. Second, the removal of necrotic masses improves drug delivery to remaining well-vascularized cells. Third, small residual tumor implants should be faster growing and therefore more susceptible to chemotherapy (see Chap. 27). Fourth, reducing the numbers of cancer cells should require fewer cycles of chemotherapy and reduce the chances of chemoresistance. Finally, removal of bulky disease potentially enhances the immune system.

Whether any of these supposed advantages to debulking are actually clinically relevant is debatable (Covens, 2000). However, because of the presumed benefits, primary surgical cytoreduction generally is performed whenever feasible clinically. Since the goal is maximal resection of ovarian cancer and all metastatic disease, laparoscopic surgery has virtually no role. Instead, a variety of procedures may be required to achieve minimal residual disease.

Surgical Approach to Cytoreductive Surgery

Typically, a vertical incision is recommended to provide access to the entire abdomen. Patients with advanced disease do not require peritoneal washings or cytologic assessment of fluid, but often several liters of ascites will need to be evacuated to improve access. Next, the abdomen is explored carefully to quickly determine if optimal debulking is feasible. Limited surgical evaluation is preferable to extensive debulking if it is obvious that tumors larger than 2 cm will be left behind. If hysterectomy and BSO are not possible, a biopsy of the ovary and sampling of the endometrium must be performed. However, if disease is resectable, then surgery should begin with the least complicated procedure.

Often, an infracolic omentectomy can be performed and extended easily (i.e., supracolic), if necessary, to encompass the disease (see Section 43-12, Omentectomy). A frozen section then may be obtained to confirm the presumptive diagnosis of epithelial ovarian cancer. The pelvis is assessed next. Usually, a total abdominal hysterectomy and BSO are sufficient. However, when the tumor is confluent or invading the rectosigmoid, an en bloc resection (see Section 43-11, En Bloc Pelvic Resection), low anterior resection (see Section 43-19, Low Anterior Resection), or modified posterior pelvic exenteration (see Section 43-5, Posterior Pelvic Exenteration) may be required.

Patients with abdominal tumor nodules that are less than 2 cm in size (apparent stage IIIB) must have bilateral pelvic and para-aortic node biopsies (see Sections 43-9, Pelvic Lymphadenectomy and 43-10, Para-Aortic Lymphadenectomy). In patients with stage IV disease and those with abdominal tumor nodules at least 2 cm in size (already stage IIIC disease), nodal dissection is not necessarily required. Histologically confirmed metastatic lymph nodes eliminates the need for further sampling (Whitney, 2005). However, if sampling is not performed, a significant percentage of patients will have unrecognized macroscopic nodal disease (Eisenkop, 2001).

To achieve optimal surgical cytoreduction also may require a variety of other procedures, including splenectomy (see Section 43-13, Splenectomy), diaphragm stripping/resection (see Section 43-14, Diaphragmatic Surgery), and small or large bowel resection (see Sections 43-16, Large Bowel Resection and 43-18, Small Bowel Resection). For diagnostic purposes, and since it is a frequent site of disease, an appendectomy is also commonly included (see Section 43-21, Appendectomy).

INTERVAL CYTOREDUCTIVE SURGERY

Many patients do not undergo initial optimal surgical debulking (Everett, 2006). In some cases, imaging studies may suggest unresectable disease. Other patients may be too medically compromised, may not have received initial care by a gynecologic oncologist, or may have large-volume "suboptimal" residual disease despite attempted debulking. In such circumstances, an "interval" cytoreductive surgery may be an option after three to four courses of chemotherapy have shrunk the tumor.

PRIMARY CHEMOTHERAPY

Advanced ovarian cancer is considered to be relatively sensitive to cytotoxic agents. Largely due to recent advances in identifying active drugs, the duration of survival among patients has increased over the past two decades. Despite such improvements, fewer than 20 percent will be cured.

Intravenous Chemotherapy

Platinum-based chemotherapy is the foundation of systemic treatment of ovarian cancer. In two large collaborative group trials (GOG protocol 158 and Arbeitsgemeinschaft GynÃ¤kologische Onkologie [AGO] protocol OVAR-3), the combination of carboplatin and paclitaxel was easier to administer, similarly efficacious, and less toxic (du Bois, 2003; Ozols, 2003). As a result, the most widely used intravenous (IV) regimen in the United States is six courses of carboplatin and paclitaxel. If additional cycles are required to achieve clinical remission, this suggests relative tumor chemoresistance and usually leads to an earlier relapse. In Europe, single-agent carboplatin is often used based on two large phase III trials of the International Collaborative Ovarian Neoplasm (ICON) group, which did not detect a survival advantage for combination chemotherapy (The ICON Collaborators, 1998; The ICON Group, 2002).

Although the combination of carboplatin and paclitaxel undoubtedly is effective, the addition of a third cytotoxic agent has been postulated to further improve outcome. Unfortunately, the preliminary analysis of a recent phase III trial failed to demonstrate any superiority compared with the control group (du Bois, 2006).

Intraperitoneal Chemotherapy

In January 2006, the National Cancer Institute issued a rare clinical announcement encouraging the use of intraperitoneal (IP) chemotherapy (National Cancer Institute, 2007b). This coincided with the publication of results from a phase III GOG trial (protocol 172) of optimally debulked stage III ovarian cancer patients who were randomly assigned to receive either intravenous or combination IV/IP paclitaxel and cisplatin chemotherapy (Table 35-7). The median duration of overall survival was 66 months in the IV/IP group compared with 50 months in the intravenous treatment group (Armstrong, 2006). Despite this dramatic improvement in survival, many clinicians still consider IP chemotherapy to be an experimental treatment (Gore, 2006).

Table 35-7 Intraperitoneal Chemotherapy Regimen for Ovarian Cancer

Day 1	Paclitaxel 135 mg/m^2 IV over 24 h
Day 2	Cisplatin 100 mg/m^2 IP
Day 8	Paclitaxel 60 mg/m^2 IP

IV = intravenous; IP = intraperitoneal. From Armstrong, 2006, with permission.

The theoretical advantages of IP chemotherapy are dramatic (see Chap. 27, Route of Administration). In general, epithelial ovarian cancer spreads mainly along peritoneal surfaces. In postoperative patients with minimal residual disease, a much higher dose of chemotherapy can be achieved at the tumor site by administration directly into the abdomen (Alberts, 1996; Markman, 2001).

Obviously, not every woman with advanced ovarian cancer is an appropriate candidate for IP chemotherapy. Stage IV patients and those with large-volume residual disease are least likely to benefit. In addition, toxicity is generally higher with IP therapy, catheter-related problems are common, and the true survival advantage remains controversial (Walker, 2006). Regardless, the current consensus is that IP therapy certainly should be considered for low-volume, optimally debulked stage III disease (Morgan, 2006). However, the choice to receive or not receive IP chemotherapy ultimately should be a decision made by an informed patient (Alberts, 2006).

In light of the National Cancer Institute clinical announcement and ensuing debate, new IP regimens are being tested currently. Phase I trials of new IP combinations are being conducted in an effort to develop a regimen with more acceptable toxicity. For example, phase I trials of dose-escalating IP carboplatin are underway through the GOG. It is anticipated that these data will shape future applications of ovarian cancer IP therapy.

Management of Patients in Remission

In most women with advanced ovarian cancer, the combination of surgery and platinum-based chemotherapy will result in clinical remission (normal examination, CA125 levels, and CT scan findings). However, up to 80 percent will relapse eventually and die from disease progression. Lower CA125 levels (i.e., single-digit values) generally are associated with fewer relapses and longer survival (Juretzka, 2007). Since most patients achieving remission will have residual, clinically occult, drug-resistant cells, several options are appropriate to consider. Unfortunately, there is no solid proof that any intervention is beneficial.

SURVEILLANCE

After completion of treatment, patients should be followed regularly with examinations and CA125 determinations, as in early-stage disease. To monitor advanced ovarian cancer patients, imaging tests may be indicated more frequently. In general, clinicians should maintain a more heightened suspicion for relapse.

SECOND-LOOK SURGERY

The "gold standard" for identifying residual disease is a second-look laparotomy. In general, the main indications are to assess the completeness of response and to resect residual tumor.

A true second-look operation consists of several steps. First, ascitic fluid or cytologic washings should be collected unless biopsy-proven disease is discovered. Second, all peritoneal surfaces must be examined visually, including direct inspection of the diaphragm, to aid removal of any suspicious nodules, adhesions, or tumors. Third, in the absence of gross disease, routine biopsies are performed from peritoneal surfaces and residual omentum. Finally, pelvic and para-aortic nodal sampling is required unless it was performed initially and no disease was found (Whitney, 2005). Second-look laparoscopy is an acceptable, less morbid alternative for selected patients (Husain, 2001; Littell, 2006).

For numerous reasons, however, neither type of second-look surgery is performed routinely. Although nonrandomized studies occasionally have reported a clinical advantage to identifying patients with residual disease, two European multicenter randomized trials of second-look laparotomy failed to demonstrate survival benefit (Luesley, 1988; Nicoletto, 1997). In addition, a recent nonrandomized comparison of patients from a prior GOG trial who had undergone second-look surgery was not associated with longer survival (Greer, 2005).

In summary, second-look laparotomy serves primarily as a useful early endpoint in assessing the effectiveness of treatment within an experimental protocol. Otherwise, no prospective clinical trials have demonstrated a survival advantage. Second-look surgery does have prognostic value because a procedure that reveals no recurrent disease is associated with an improved survival rate. In summary, the additional morbidity and cost must be weighed against the expected benefit for an individual patient (American College of Obstetricians and Gynecologists, 1996).

MAINTENANCE CHEMOTHERAPY

There is limited evidence to suggest any advantage for additional treatment in women who achieve clinical remission after six courses of platinum-based chemotherapy. However, because of the known high rate of recurrence, several agents have been tested as maintenance therapy, also termed *consolidation therapy,* in nonrandomized studies. Of these agents, lower-dose paclitaxel or CT-2103 (Xyotax, a conjugated paclitaxel with a more favorable toxicity profile, Cell Therapeutics, Seattle, WA) are being evaluated to determine if they actually can reduce the death rate compared with no maintenance therapy. The GOG currently is conducting a phase III trial of these drugs in women with advanced ovarian cancer who achieved a clinical remission after standard platinum-based chemotherapy (protocol 212).

In the meantime, monthly paclitaxel for 12 cycles is the only maintenance therapy to demonstrate any clinical advantage. Interestingly, this benefit appeared to be limited mainly to patients with the lowest CA125 levels and presumably, the lowest tumor

burden at study entry (Markman, 2006). In addition, cumulative toxicity, most notably neuropathy, can be substantialâ€”resulting in frequent dose reductions (Markman, 2003).

Radiation Therapy

In the United States, patients in remission after primary therapy are rarely treated with whole abdominal radiotherapy because of unproven benefit and fears of excessive toxicity such as radiation enteritis (Sorbe, 2003). However, the long-term effectiveness of this consolidation strategy is comparable with that achieved in women treated with other modalities. As a result, it may be considered for selected patients with microscopic disease detected at second-look surgery (Morgan, 2006). In general, this practice is much more common in Europe (Petit, 2007).

Prognostic Factors

The overall 5-year survival rate of all stages of epithelial ovarian cancer is 50 percent, far lower than uterine (80 percent) or cervical cancer (70 percent). Surgical stage is the most important variable, but relative survival also varies by age (Table 35-8). Specifically, women younger than 65 years are approximately twice as likely to survive 5 years following diagnosis. Interestingly, BRCA mutation carriers also have a better prognosis chiefly due to increased platinum sensitivity (Cass, 2003). Additional prognostic factors are shown in Table 35-9.

Table 35-8 Epithelial Ovarian Cancer 5-Year Survival Rates for Each FIGO Stage (*n* = 4,911 Patients)

Stage	5-Year Survival (%)
I	86
II	70
III	34
IV	19

FIGO = International Federation of Gynecology and Obstetrics. From Heintz, 2006, with permission.

Table 35-9 Prognostic Factors for Ovarian Cancer
Good performance status
Cell type other than mucinous and clear cell
Well-differentiated tumor
Smaller disease volume prior to any surgical debulking
Absence of ascites
Smaller residual tumor following primary cytoreductive surgery

From National Cancer Institute, 2007a, with permission.

Due to several advances, there has been recent improvement in the overall survival of women with ovarian cancer (Chan, 2006). By employing a more aggressive surgical approach, the rate of optimal primary cytoreduction has been increased (Chi, 2004). The activity of paclitaxel in combination with a platinum agent also has improved survival rates for many. The recent use of IP chemotherapy demonstrated the longest duration of survival for stage III patients among all randomized phase III trials conducted by the GOG. Regardless, treatment of recurrent disease is particularly important because most patients will relapse ultimately.

Management of Recurrent Ovarian Cancer

Gradual elevation of the CA125 level is usually the first sign of relapse. Tamoxifen may be administered frequently when this is the only evidence for disease progression because it has some activity in treating recurrent disease, and toxicity is minimal. Alternatively, patients may be offered participation in a clinical trial, started on cytotoxic chemotherapy, or observed until clinical symptoms arise. Without treatment, the recurrence usually will become obvious clinically within 2 to 6 months. Almost invariably, the tumor will be located somewhere within the abdomen.

Women who progress during primary chemotherapy are classified as having *platinum-refractory disease.* Those who relapse within 6 months have *platinum-resistant ovarian cancer* (National Cancer Institute, 2007d). In general, patients in either category have a dismal prognosis, and palliative nonplatinum chemotherapy is effectively the only option. Participation in an experimental clinical trial should be offered whenever possible. Otherwise, response rates typically range from 10 to 15 percent using conventional cytotoxic drugs such as paclitaxel, pegylated liposomal doxorubicin (Doxil, Ortho Biotech Products, Bridgewater, NJ), docetaxel (Taxotere, Sanofi-Aventis, Bridgewater, NJ), topotecan (Hycamtin, GlaxoSmithKline, Philadelphia, PA), or gemcitabine (Gemzar, Eli Lilly, Indianapolis, IN).

Women who relapse more than 6 to 12 months after completion of primary therapy are considered *platinum-sensitive.* These patients, especially those in prolonged remission beyond 18, 24, or 36 months, have the greatest number of potential options, which are subsequently discussed (Morgan, 2006).

SECONDARY CYTOREDUCTIVE SURGERY

Although patient selection is somewhat arbitrary, the best candidates for secondary cytoreductive surgery have (1) platinum-sensitive disease, (2) a prolonged disease-free interval, (3) a solitary site of recurrence, and (4) no ascites (Chi, 2006). To achieve a maximal survival benefit, debulking must result in minimal residual disease (Harter, 2006). However, about half of patients will be explored without achieving this goal. Further, as in primary surgical cytoreduction, the overall survival benefit of this approach has never been studied in a randomized clinical trial.

SALVAGE CHEMOTHERAPY

Regardless of whether patients undergo additional surgery, retreatment with a platinum drug is the treatment of choice for patients with recurrent platinum-sensitive ovarian cancer. Carboplatin combined with either paclitaxel or gemcitabine has demonstrated superiority compared with carboplatin alone (Parmar, 2003; Pfisterer, 2006). However, giving these drugs sequentially as single agents might be equally successful and less toxic (National Cancer Institute, 2007d). Thereafter, pegylated liposomal doxorubicin may be the most appropriate choice (Gordon, 2001). Topotecan and docetaxel are other commonly used agents. Recently, the biologic agent bevacizumab (Avastin, Genentech, South San Franscisco, CA) also has demonstrated promising activity (Monk, 2006).

Regardless of which regimen is selected initially, re-evaluation usually should follow two to three cycles of chemotherapy to determine the clinical benefit (Morgan, 2006). Nonresponders should be changed to a different regimen that may be more efficacious.

Since the type of chemotherapy is based on overall response rates for all the histologic variants of epithelial ovarian cancer, it would seem plausible that targeting therapy for an individual patient's disease might be more effective than selecting a drug empirically. In vitro chemosensitivity testing is used occasionally for this purpose. In principle, different agents are tested against the patient's tumor, and the chemotherapeutic drug demonstrating the best response should result in a better outcome. Unfortunately, this approach lacks demonstrable clinical efficacy (Morgan, 2006).

Palliation of End-Stage Ovarian Cancer

During treatment, intermittent episodes of partial small and large bowel obstruction are common. However, at some point patients with recurrent disease will develop worsening symptoms that warrant re-evaluation of their overall treatment strategy.

Bowel obstruction that does not resolve with nasogastric suction can be managed in two very different ways. Frequently, a patient may desire an aggressive approach with surgical intervention, initiation of total parenteral nutrition (TPN), and continued

chemotherapy. Ideally, a colostomy (see Section 43-15, Colostomy), ileostomy (see Section 43-17, Ileostomy), or intestinal bypass (see Section 43-20, Intestinal Bypass) will return reasonably normal bowel function. Unfortunately, a satisfactory surgical result is often impossible because of multiple sites of partial or complete obstruction. In addition, successful palliation rarely is achieved when the transit time is prolonged by diffuse peritoneal carcinomatosis or when the anatomy requires a bypass that results in the short bowel syndrome (National Cancer Institute, 2007d). Further, recovery often is complicated by an enterocutaneous fistula, reobstruction, or other morbid event (Pothuri, 2004). For some patients, the best approach to managing a refractory bowel obstruction may be placement of a palliative gastrostomy tube, IV hydration, and hospice care. The final decision about how to proceed should be based on a frank discussion. Topics include treatment options, the natural history of progressive ovarian cancer, and the realistic possibility of any further disease response by switching to a different therapy.

Another common scenario is a woman with symptomatic, rapidly reaccumulating ascitic fluid. This may be alleviated by repeated paracenteses or placement of an indwelling peritoneal catheter (Pleurx, Denver Biomedical, Golden, CO). Similarly, a refractory malignant pleural effusion usually can be managed by thoracentesis, pleurodesis, or indwelling peritoneal catheter placement.

Although these procedures and others may be appropriate in selected patients, the inability to halt disease progression should be acknowledged. In addition, any intervention has the potential to result in an unanticipated catastrophic complication. Overall, palliative procedures are used most compassionately when incorporated into the overall treatment plan. For example, in a woman with stable disease and normal renal function, tumor-induced ureteral compression and hydronephrosis does not necessarily require stent placement or a nephrostomy tube.

All patients deserve a positive, hopeful, but honest approach to the management of progressive, incurable disease. Often there are unrealistic expectations about the benefit of palliative chemotherapy, but emotionally, it may be preferable to no treatment (Doyle, 2001). There is no substitute for mutual trust in the doctor-patient relationship when making sound decisions aimed at improving the quality of life of women with end-stage ovarian cancer.

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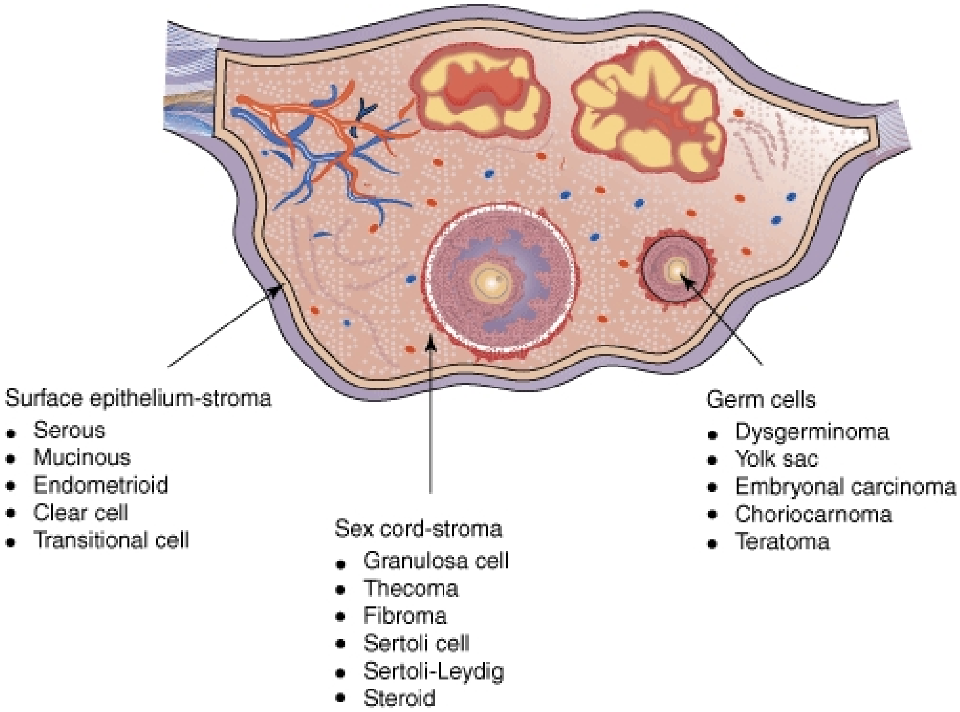
OVARIAN GERM CELL AND SEX CORDÂ€“STROMAL TUMORS: INTRODUCTION

Three major categories account for virtually all malignant ovarian tumors. Organization of these groups is based on the anatomic structures from which the tumors originate (Fig. 36-1). Epithelial ovarian cancers account for 90 to 95 percent of malignant ovarian tumors (see Chap. 35). Germ cell and sex cordâ€“stromal ovarian tumors account for the remaining 5 to 10 percent and have unique qualities that require a special management approach (Quirk, 2005).

FIGURE 36-1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Origins of the three main types of ovarian tumors. *(From Chen, 2003, with permission.)*

MALIGNANT OVARIAN GERM CELL TUMORS

Germ cell tumors arise from the ovary's germinal elements and comprise a third of all ovarian neoplasms. The mature cystic teratoma, also called *dermoid cyst,* is by far the most common subtype. This accounts for 95 percent of all germ cell tumors and is clinically benign (see Chap. 9, Mature Cystic Teratoma (Benign Cystic Teratoma or Dermoid Cyst)). In contrast, malignant germ cell tumors comprise fewer than 5 percent of malignant ovarian cancers in Western countries and include *dysgerminoma, yolk sac tumor, immature teratoma,* and other less common types.

Three features typically distinguish malignant germ cell tumors from epithelial ovarian cancers. First, individuals typically present

at a younger age, usually in their teens or early twenties. Second, most have stage I disease at diagnosis. Third, prognosis is excellentâ€”even for those with advanced diseaseâ€”due to exquisite tumor chemosensitivity.

Fertility-sparing surgery is the primary treatment for women seeking future pregnancy, and most will not require postoperative chemotherapy.

Epidemiology

The age-adjusted incidence of malignant ovarian germ cell tumors in the United States is much lower (0.4 per 100,000 women) than that of epithelial ovarian carcinomas (15.5) but twice that of sex cordâ€"stromal tumors (0.2) (Quirk, 2005). Malignant germ cell tumors generally are not thought to be inherited, but familial cases are reported rarely (Galani, 2005; Stettner, 1999).

These tumors are the most common ovarian malignancies diagnosed during childhood and adolescence, although only 1 percent of all ovarian cancers develop in these age groups. At age 20, however, the incidence of epithelial ovarian carcinoma begins to rise and exceeds that of germ cell tumors (Young, 2003).

Diagnosis

SIGNS AND SYMPTOMS

The signs and symptoms associated with these tumors are varied, but in general, most arise from tumor growth and hormones the tumor produces. Subacute abdominal pain is the most common symptom and reflects rapid growth of a large, unilateral tumor undergoing capsular distention, hemorrhage, or necrosis. In addition, cyst rupture, torsion, or intraperitoneal hemorrhage leads to an acute abdomen in 10 to 20 percent of patients (De Backer, 2006). In more advanced disease, ascites may develop and cause abdominal distention. Because of the hormonal changes that frequently accompany these tumors, menstrual irregularities also may develop. Although most individuals note one or more of these symptoms, one quarter of individuals are asymptomatic, and a pelvic mass is noted unexpectedly during physical or sonographic examination (Curtin, 1994).

HISTORY

Individuals typically seek care within 1 month of the onset of abdominal complaints, although some note subtle waxing and waning symptoms for more than a year. Most young women with these tumors are nulligravidas with normal periods, but as discussed later, individuals with dysgenetic gonads are at significant risk for development of these tumors (Curtin, 1994). Therefore, adolescents who present with pelvic masses and delayed menarche should be evaluated for gonadal dysgenesis (see Chap. 16, Chromosomal Defects).

DIFFERENTIAL DIAGNOSIS

Vague pelvic symptoms are common during adolescence due to initiation of ovulation and menstrual cramping. As a result, early symptoms may be dismissed. Moreover, young girls may be silent about changes to their normal pattern, fearful of their significance. Early symptoms can be misinterpreted as those of pregnancy and acute pain may be confused with appendicitis.

Finding an adnexal mass is the first diagnostic step. In most cases, sonography can display those qualities which typically characterize benign and malignant ovarian masses adequately (see Table 9-4). Functional ovarian cysts are vastly more common in young women, and once identified as hypoechoic, smooth-walled cysts may be observed by sonography. In contrast, malignant germ cell tumors are usually larger with solid components. Elevated serum human chorionic gonadotropin (hCG) or alpha-fetoprotein (AFP) tumor markers may narrow the diagnostic possibilities and suggest the potential need for surgical staging.

PHYSICAL EXAMINATION

Distinguishing physical findings typically are lacking in individuals with malignant germ cell tumors. A palpable mass on pelvic examination is the most common finding. In children and adolescents, however, completing a comprehensive pelvic or transvaginal sonographic examination can be difficult and may lead to diagnostic delay (see Chap. 14, Ovarian Tumors). Accordingly, premenarchal patients may require examination under anesthesia to assess a suspected adnexal tumor adequately. The remainder of the physical examination should search for signs of ascites, pleural effusion, and organomegaly.

LABORATORY TESTING

Patients with a suspected malignant germ cell tumor should have serum hCG and AFP tumor marker determination, a complete blood count, and liver function tests drawn before treatment. Alternatively, the appropriate tumor marker determinations may be ordered in the operating room if the diagnosis was not suspected previously (Table 36-1). Preoperative karyotyping of young women with primary amenorrhea and a suspected germ cell tumor can clarify whether both ovaries should be removed, as in the case of women with gonadal dysgenesis (Hoepffner, 2005).

Table 36-1 Serum Tumor Markers in Malignant Ovarian Germ Cell Tumors

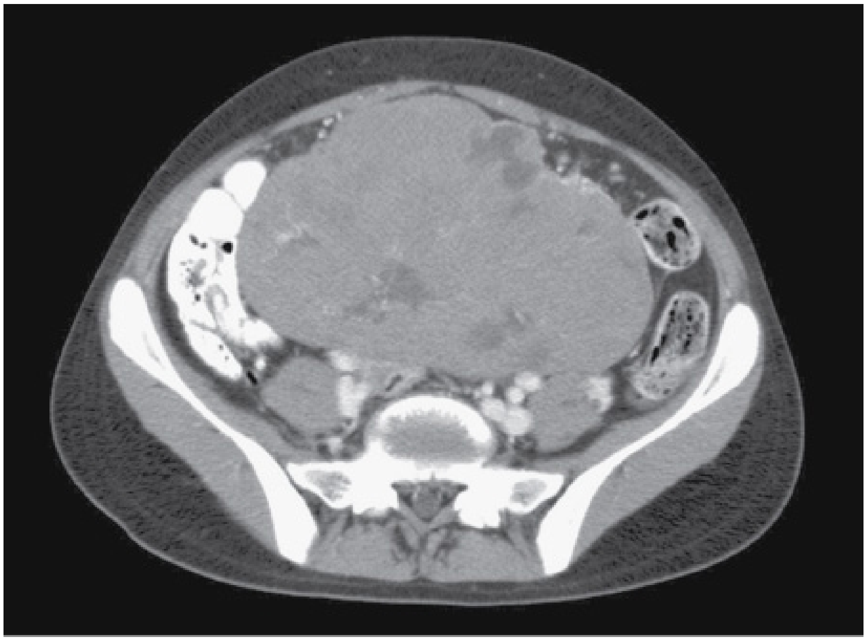
Histology	AFP	hCG
Dysgerminoma	â€“	Â±
Yolk sac tumor	+	â€“
Immature teratoma	Â±	â€“
Choriocarcinoma	â€“	+
Embryonal carcinoma	+	+
Mixed germ cell tumor	Â±	Â±
Polyembryoma	Â±	Â±

AFP = alphafetoprotein; hCG = human chorionic gonadotropin.

IMAGING

Mature cystic teratomas (dermoid cysts) usually display characteristic features when imaged with sonography or computed tomographic (CT) scanning (see Chap. 9, Pathology). However, the appearance of malignant germ cell tumors differs, and a multilobulated complex ovarian mass is typical (Fig. 36-2). Moreover, prominent blood flow in the fibrovascular septa may be seen using color-flow Doppler sonography and suggests the likelihood of malignancy (see Fig. 35-6). (Kim, 1995). Additional preoperative CT scanning or magnetic resonance (MR) imaging is not mandatory because the abdomen will be explored during surgery. However, chest radiography is warranted to search for tumor metastases in the lungs or mediastinum.

FIGURE 36-2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Computed tomographic (CT) scan of a germ cell tumor.

DIAGNOSTIC PROCEDURES

Sonographically or CT-guided percutaneous biopsy has no role in the management of patients with an ovarian mass suspicious for malignancy. Surgical resection is required for definitive tissue diagnosis, staging, and treatment. The surgeon should request a frozen section evaluation to confirm the diagnosis, but discrepancies between frozen-section interpretations and the final paraffin histology are commonplace (Kusamura, 2000). In addition, specific immunostaining is often required to resolve equivocal cases (Cheng, 2004; Ramalingam, 2004; Ulbright, 2005).

Role of the Generalist

Most patients will be seen initially by a generalist in obstetrics and gynecology. Initial symptoms may point to the more common functional ovarian cyst. Persistent symptoms or an enlarging pelvic mass, however, should prompt sonographic evaluation. If a complex ovarian mass with solid features is noted in this young age group, then measurement of serum hCG and AFP levels and referral to a gynecologic oncologist for primary surgical management should ensue.

When a specialist is unavailable or the diagnosis is not anticipated beforehand, intraoperative decisions are crucial to treat the patient adequately without compromising future fertility. Peritoneal washings are obtained and set aside before proceeding with dissection of any suspicious adnexal mass. The washings can be discarded later if malignancy is excluded. Initially, the decision to perform cystectomy or oophorectomy depends on the clinical circumstances (see Chap. 9, Cystectomy Versus Oophorectomy). Regardless, the entire adnexa should be removed once a malignant ovarian germ cell tumor is diagnosed. A generalist in obstetrics and gynecology should request intraoperative assistance with staging from a gynecologic oncologist or refer the patient postoperatively if a specialist is not immediately available. At a minimum, the abdomen should be explored. Palpation of the omentum and upper abdomen and inspection of the pelvisâ€”especially the contralateral ovaryâ€”are easy to perform and document.

Pathology

CLASSIFICATION

The modified World Health Organization (WHO) classification of ovarian germ cell tumors is presented in Table 36-2 (Nogales,

2003). These tumors are composed of several histologically different tumor types derived from primordial germ cells of the embryonic gonad. There are two major categories: primitive malignant germ cell tumors (dysgerminomas) and teratomasâ€”almost all of which are accounted for by mature cystic teratomas (dermoid cysts).

Table 36-2 Modified World Health Organization Classification of Ovarian Germ Cell Tumors
Primitive germ cell tumors
Dysgerminoma
Yolk sac tumor (endodermal sinus tumor)
Embryonal carcinoma
Polyembryoma
Nongestational choriocarcinoma
Teratomas
Immature
Mature
Solid
Cystic (dermoid cyst)
Monodermal and highly specialized
Thyroid tumors (struma ovarii: benign or malignant)
Carcinoids
Neuroectodermal tumors
Carcinomas (squamous cell or adeno-)
Melanocytic group
Sarcomas
Sebaceous tumors
Mixed forms (tumors composed of two or more of the above pure types)

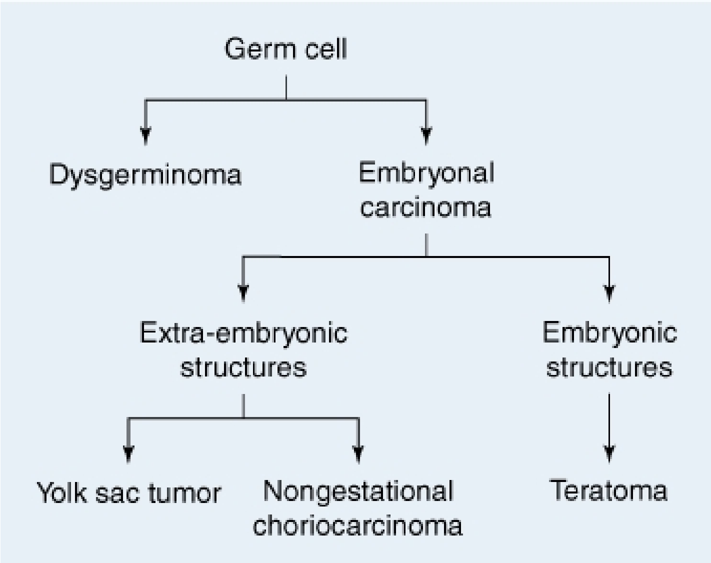
HISTOGENESIS

Primitive germ cells migrate from the wall of the yolk sac to the gonadal ridge. As a result, most germ cell tumors arise in the gonad. Rarely, these tumors may develop primarily in extragonadal sites such as the central nervous system, mediastinum, or retroperitoneum (Hsu, 2002).

Ovarian germ cell tumors have a variable pattern of differentiation (Fig. 36-3). Dysgerminomas are primitive neoplasms that do not have the potential for further differentiation. Embryonal carcinomas are composed of multipotential cells that are capable of further differentiation. This lesion is the precursor of several other types of extraembryonic (yolk sac tumor, choriocarcinoma) or

embryonic (teratoma) germ cell tumors. The process of differentiation is dynamic, and the resulting neoplasms may be composed of different elements showing various stages of development (Teilum, 1965).

FIGURE 36-3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Differentiation pathway of germ cell tumors.

Dysgerminoma

RISK FACTORS

Half of all malignant ovarian germ cell tumors are dysgerminomas. These tumors are the most common ovarian malignancy detected during pregnancy. This is believed to be an age-related coincidence, however, and not due to some particular characteristic of gestation.

Five percent of dysgerminomas are discovered in phenotypic females with karyotypically abnormal gonads, specifically, with the presence of a normal or abnormal Y chromosome (Morimura, 1998). Commonly, this group includes those with Turner syndrome mosaicism (45,X/46,XY), Klinefelter syndrome (46,XY, male pseudohermaphroditism), and Swyer syndrome (46,XY, puregonadal dysgenesis) (see Chap. 18, Male Pseudohermaphroditism (Category II)). The dysgenetic gonads of these individuals often contain gonadoblastomas, which are benign germ cell neoplasms. These tumors may regress or alternatively may undergo malignant transformation, most commonly to dysgerminoma. Because approximately 40 percent of gonadoblastomas in these individuals undergo malignant transformation, both ovaries should be removed (Hoepffner, 2005; Pena-Alonso, 2005).

CLINICAL FINDINGS

Dysgerminomas are the only germ cell malignancy with a significant rate of bilateral ovarian involvementâ€”15 to 20 percent. Half of patients with bilateral lesions will have grossly obvious disease, whereas cancer in the remainder will be detected only microscopically. Five percent of women have elevated serum hCG levels due to intermingled syncytiotrophoblasts. Similarly, serum lactate dehydrogenase (LDH) and the isoenzymes LDH-1 and LDH-2 also may be useful in monitoring individuals for disease recurrence (Pressley, 1992; Schwartz, 1988).

Dysgerminomas have a variable gross appearance but in general are solid, pink to tan to cream-colored, lobulated masses. Microscopically, there is a monotonous proliferation of large, rounded, polyhedral clear cells that are rich in cytoplasmic glycogen and contain uniform central nuclei with one or a few prominent nucleoli. The tumor cells resemble closely the primordial germ cells

of the embryo and are identical histologically to seminoma of the testis.

TREATMENT

Treatment of dysgerminoma involves fertility-sparing surgery with unilateral salpingo-oophorectomy (USO) and careful surgical staging of disease (Ayhan, 2000). Preservation of the contralateral ovary, however, leads to "recurrent" dysgerminoma in 5 to 10 percent of retained gonads over the next 2 years. This finding in many cases is thought to reflect the high rate of clinically occult disease in the remaining ovary rather than true recurrence. Indeed, 75 percent of recurrences develop within the first year of diagnosis. Other common recurrence sites are within the peritoneal cavity or retroperitoneal lymph nodes. Despite this significant incidence of recurrent disease, a conservative surgical approach does not adversely affect long-term survival because of this cancer's sensitivity to chemotherapy.

Dysgerminomas have the best prognosis of all malignant ovarian germ cell tumor variants (Lai, 2005; Yilmaz, 2003). Three quarters are stage I at diagnosis, and the 5-year survival exceeds 95 percent (Table 36-3). Even those with advanced disease have high survival rates following chemotherapy. For example, those with stage IIâ€“IV disease have an 85 to 90 percent survival rate with platinum-based agents. However, advanced stage remains the most important prognostic factor (Ayhan, 2000; Lai, 2005).

Table 36-3 Stage and Survival of Common Malignant Ovarian Germ Cell Tumors

	Dysgerminoma	**Yolk Sac Tumor**	**Immature Teratoma**
Stage at diagnosis			
I	75%	67%	50â€“60%
IIâ€“IV	25%	33%	40â€“50%
Five-year survival			
Stage I	>95%	80%	90â€“95%
Stage IIâ€“IV	85â€“90%	<10%	75â€“80%

Sources for survival figures are referenced within the text.

Yolk Sac Tumors

CLINICAL FINDINGS

Yolk sac tumors account for 20 percent of all malignant ovarian germ cell tumors. These lesions previously were called *endodermal sinus tumors,* but the terminology has been revised recently. A third of patients are premenarchal at the time of initial presentation. Involvement of both gonads is rare, and the other ovary usually is involved with metastatic disease only when there are other metastases in the peritoneal cavity.

Grossly, these tumors form solid masses that are more yellow and friable than dysgerminomas. They are often focally necrotic and hemorrhagic, with cystic degeneration and rupture. The microscopic appearance of yolk sac tumors is often diverse. The most common appearance, the reticular pattern, reflects extraembryonic differentiation, with formation of a network of irregular, anastomosing spaces that are lined by primitive epithelial cells. *Schiller-Duval bodies* are pathognomonic when present. These characteristically have a single papilla that is lined by tumor cells and contains a central vessel. Alpha-fetoprotein is commonly produced by these tumors. As a result, yolk sac tumors usually contain cells that stain immunohistochemically for AFP, and serum levels can serve as a reliable tumor marker in posttreatment surveillance.

TREATMENT

Yolk sac tumors are the most deadly malignant ovarian germ cell tumor type. All patients are treated with chemotherapyâ€”regardless of stage. Two thirds present with stage I disease and have a 5-year survival of 80 percent.

Unfortunately, yolk sac tumors have a propensity for rapid growth, peritoneal spread, and distant hematogenous dissemination to the lungs. Accordingly, individuals with stage IIâ€“IV disease have a dismal survival rate of less than 10 percent. Patients die within 2 years of diagnosis in greater than 90 percent of these more advanced cases (Ayhan, 2005; Fujita, 1993). Poor prognostic factors include an advanced initial cancer stage, residual disease following surgical staging, and ascites (Nawa, 2001).

Other Primitive Germ Cell Tumors

The rarest subtypes of nondysgerminomatous tumors typically are mixed with other more common variants and usually are not found in pure form.

EMBRYONAL CARCINOMA

Patients diagnosed with embryonal carcinoma characteristically are younger, with a mean age of 14 years, than those having other types of germ cell tumors. Epithelial cells resembling those of the embryonic disk comprise these primitive tumors. The solid disorganized sheets of large anaplastic cells, gland-like spaces, and papillary structures are distinctive and allow easy identification of these tumors (Ulbright, 2005). Although dysgerminomas are the most common germ cell tumor resulting from malignant transformation of gonadoblastomas in women with dysgenetic gonads, occasionally embryonal "testicular" tumors also may originate (LaPolla, 1990). Embryonal carcinomas typically produce hCG, and 75 percent also secrete AFP.

POLYEMBRYOMA

Polyembryomas characteristically contain many embryo-like bodies, each with a small central "germ disk" positioned between two cavities, one mimicking an amnionic cavity and the other a yolk sac. Syncytiotrophoblast giant cells are frequent, but elements other than the embryoid bodies should constitute less than 10 percent of the tumor for the *polyembryoma* designation to be used. Conceptually, these tumors may be viewed as a bridge between the primitive (dygerminoma) and differentiated (teratoma) germ cell tumor types. For this reason, polyembryomas often are considered to be the most immature of all teratomas (Ulbright, 2005). Serum AFP or hCG levels or both may be elevated in these individuals due to the yolk sac and syncytial components (Takemori, 1998).

CHORIOCARCINOMA

Primary ovarian choriocarcinoma arising from a germ cell appears similar to gestational choriocarcinoma with ovarian metastases. The distinction is important because nongestational tumors have a poorer prognosis (Corakci, 2005). The detection of other germ cell components indicates nongestational choriocarcinoma, whereas a concomitant or proximate pregnancy suggests a gestational form (Ulbright, 2005). Clinical manifestations are common and result from the high hCG levels produced by these tumors. These elevated levels may induce sexual precocity in prepubertal girls or menometrorrhagia in reproductive-aged women (Oliva, 1993).

MIXED GERM CELL TUMORS

Ovarian germ cell tumors have a mixed pattern of cellular differentiation in 10 percent of patients. Dysgerminoma is the most common component and typically is seen with yolk sac tumor or immature teratoma or both. The frequency of bilateral ovarian involvement depends on the presence or absence of a dysgerminoma component and increases when present. However, treatment and prognosis are determined by the nondysgerminomatous component (Low, 2000). For this reason, elevated serum hCG and particularly AFP levels in a woman with a presumed pure dysgerminoma should prompt a search for other germ cell components by more extensive histologic evaluation (Aoki, 2003).

Immature Teratomas

CLINICAL FINDINGS

Immature teratomas account for 20 percent of all malignant ovarian germ cell tumors and approximate the frequency of yolk sac tumors. They are composed of tissues derived from the three germ layers: ectoderm, mesoderm, and endoderm. The presence of immature or embryonal structures, however, distinguishes these tumors from the much more common and benign mature cystic teratoma (dermoid cyst). Bilateral ovarian involvement is rare, but 10 percent of patients have a mature teratoma in the contralateral ovary. Tumor markers often are negative unless the immature teratoma is comingled with other germ cell tumor types. Of these, AFP, cancer antigen 125 (CA125), CA-19-9, and carcinoembryonic antigen (CEA) may be helpful in some cases (Li,

2002).

On gross external inspection, these tumors appear as large, rounded or lobulated, soft or firm masses. They frequently perforate the ovarian capsule and invade locally. The most frequent site of dissemination is the peritoneum and much less commonly the retroperitoneal lymph nodes. With local invasion, surrounding adhesions commonly form and are thought to explain the lower rates of torsion with this tumor compared with that of its benign mature counterpart (Cass, 2001). On cut surface, the interior typically is solid with intermittent cystic areas, but occasionally the reverse is seen, with solid nodules present only in the cyst wall. Solid parts may correspond to the immature elements, cartilage, bone, or a combination of these, whereas cystic areas are filled with serous or mucinous fluid or sebaceous material and hair.

Microscopic examination reveals a disorderly mixture of tissues. Of the immature elements, neuroectodermal tissues almost always predominate and are arranged as primitive tubules and sheets of small, round, malignant cells that may be associated with glia formation. The diagnosis typically is difficult to confirm at frozen section evaluation, and most tumors will be confirmed only on final pathologic review. Tumors are graded 1 to 3 primarily by the amount of immature neural tissue they contain. O'Connor and Norris (1994) analyzed 244 immature teratomas and noted significant inconsistencies in grade assignment by different observers. For this reason, they proposed changing the system to two grades: low (previously grades 1 and 2) and high (previously grade 3). This practice, however, has not been universally accepted.

TREATMENT AND PROGNOSIS

In general, survival is predicted most accurately by the histologic grade of the tumor. For example, two thirds of immature teratomas are stage I at diagnosis and have a 5-year survival rate of 90 to 95 percent (Gershenson, 1986b; O'Connor, 1994). Those with stage IA, grade 1 immature teratomas have an excellent prognosis and do not require adjuvant chemotherapy (Bonazzi, 1994; Marina, 1999). Patients with stage IIâ€"IV disease have a 70 to 80 percent 5-year survival rate (Bonazzi, 1994; Kojs, 1997; Williams, 1994a).

Unilateral salpingo-oophorectomy (USO) is the standard care for these and other malignant germ cell tumors in reproductive-aged women. Beiner and colleagues (2004), however, treated eight women with early-stage immature teratoma with ovarian cystectomy and adjuvant chemotherapy and noted no recurrences.

Immature teratomas may be associated with mature tissue implants studding the peritoneum that do not increase the stage of the tumor or diminish the prospect of survival. However, these implants of mature teratomatous elements, even though benign, are resistant to chemotherapy and can enlarge during or after chemotherapy. Termed the *growing teratoma syndrome,* these implants require second-look surgery and resection to exclude recurrent malignancy (Geisler, 1994; Umekawa, 2005).

MALIGNANT TRANSFORMATION OF MATURE CYSTIC TERATOMAS (DERMOID CYSTS)

These rare tumors are the only germ cell variants that typically develop in postmenopausal women. Malignant areas usually are found as small nodules in the cyst wall or a polypoid mass within the lumen after removal of the entire mature cystic teratoma (Pins, 1996). Squamous cell carcinoma is most common and is found in approximately 1 percent of mature cystic teratomas. Other malignant tumors identified include basal cell carcinomas, sebaceous tumors, malignant melanomas, adenocarcinomas, sarcomas, and neuroectodermal tumors. Moreover, endocrine-type neoplasms such as struma ovarii (teratoma composed mainly of thyroid tissue) and carcinoid may be found within mature cystic teratomas. These are malignant in less than 5 percent of patients. The malignant struma rarely functions at a clinically relevant level, but the carcinoid tumor does in a third of patients (Robboy, 1980; Young, 1993).

Treatment

SURGERY

A vertical abdominal incision traditionally is recommended if ovarian malignancy is suspected. However, investigators with advanced endoscopic skills have noted laparoscopy to be a safe and effective alternative for those women with small ovarian masses and apparent stage I disease (Chi, 2005). If present, ascites is evacuated and sent for cytologic evaluation. Otherwise, washings of the pelvis and paracolic gutters are collected for analysis prior to manipulation of intraperitoneal contents. Washings can be discarded later if intraoperative evaluation or frozen-section interpretation is unequivocally benign. Regardless of the

surgical approach, the entire peritoneal cavity should be systematically inspected. The ovaries should be assessed for size, tumor involvement, capsular rupture, external excrescences, and adherence to surrounding structures.

Fertility-sparing USO should be performed in all reproductive-aged women diagnosed with malignant ovarian germ cell tumors because this conservative approach in general does not adversely affect survival (Peccatori, 1995). Following USO, blind biopsy or wedge resection of a normal-appearing contralateral ovary is not recommended. For those who have completed childbearing, hysterectomy with bilateral salpingo-oophorectomy (BSO) is appropriate. In either case, following removal of the affected ovary, surgical staging by laparotomy or laparoscopy proceeds as previously described for epithelial ovarian cancer (see Chap. 35, Surgical Staging). Because of tumor dissemination patterns, lymphadenectomy is most important for dysgerminomas, whereas staging peritoneal and omental biopsies are particularly valuable for yolk sac tumors and immature teratomas (Gershenson, 1983).

Cytoreductive surgery generally is recommended for malignant ovarian germ cell tumors when extensive disease is encountered at initial surgery. Tumor debulking to a level of minimal residual disease improves the likelihood of response to chemotherapy and cure (Bafna, 2001; Nawa, 2001; Suita, 2002). The same general principles of cytoreductive surgery are applied as described for epithelial ovarian cancer (see Chap. 35, Primary Cytoreductive Surgery). Thus, minimal residual disease is considered to be that in which each remaining tumor implant measures less than 1 cm. Because of the exquisite chemosensitivity of most malignant germ cell tumors, however, surgeons may choose to be less aggressive in performing radical debulking procedures.

Many women will be referred to a gynecologic oncologist after USO with a tumor that was clinically confined to the excised ovary. For such patients, if initial surgical staging was incomplete, options may include a second surgery for primary staging, regular surveillance, or adjuvant chemotherapy. Because of its minimally invasive qualities, laparoscopy is a particularly attractive option for delayed surgical staging following primary excision and has been shown to accurately detect those women who need chemotherapy (Leblanc, 2004). Surgical staging following primary excision, however, is less important for scenarios in which chemotherapy will be administered regardless of surgical findings, such as clinical stage I yolk sac tumors and high-grade clinical stage I immature teratomas (Stier, 1996).

SURVEILLANCE

Patients with malignant ovarian germ cell tumors should be followed by careful clinical, radiologic, and serologic surveillance every 3 months for the first 2 years after completion of therapy (Dark, 1997). Ninety percent of recurrences develop within this time frame (Messing, 1992). Second-look surgery at the completion of therapy is not necessary in women with completely resected disease or in those individuals with advanced tumor that does not contain teratoma (Chambers, 1988; Gershenson, 1986a). However, incompletely resected immature teratoma is the one circumstance among all types of ovarian cancer in which patients clearly benefit from second-look surgery and excision of chemorefractory tumor (Culine, 1996; Rezk, 2005; Williams, 1994b).

CHEMOTHERAPY

Stage IA dysgerminomas and stage IA, grade 1 immature teratomas do not require additional chemotherapy. More advanced disease and all other histologic types of malignant ovarian germ cell tumors, however, are treated with combination platinum-based chemotherapy (Suita, 2002; Tewari, 2000). Successful management without postoperative chemotherapy has been reported, but adjuvant treatment generally is recommended (Chapman, 1994).

The standard regimen is a 5-day course of bleomycin, etoposide, and cisplatin (BEP) (Gershenson, 1990; Williams, 1987). Modified 2- or 3-day BEP combinations also have been shown recently to be safe and effective in pilot studies but are not used routinely in practice (Dimopoulos, 2004; Tay, 2000). For women with accurate staging and completely resected ovarian germ cell tumors, three courses of BEP will prevent recurrence in nearly all (Williams, 1994a). Carboplatin and etoposide, given in three cycles, has shown promise as an alternative for selected patients, but it warrants further study before it can be considered standard treatment (Williams, 2004). For women with incompletely resected disease, at least four courses of BEP are recommended currently (Williams, 1991).

Although no randomized clinical trials exist, the BEP regimen is considered the standard for patients with malignant ovarian germ cell tumors (Culine, 2000; Gershenson, 1990). This regimen is as effective but less toxic than a combination of cisplatin, vinblastine, and bleomycin (PVB) (Williams, 1987). Vincristine, dactinomycin, and cyclophosphamide (VAC) was another frequently

used regimen in the 1970s and 1980s, but it also has been supplanted by BEP because its sustained remission rate for advanced disease was disappointingly low (Gershenson, 1985; Wong, 1989). Because chemotherapy remains effective when used at the time of relapse, some investigators are attempting to identify additional low-risk, early-stage subgroups that may be observed postoperatively and thereby avoid treatment-related toxicity (Bonazzi, 1994; Cushing, 1999; Dark, 1997). However, before this strategy can be incorporated into general practice, additional large studies are necessary to determine relapse rates, salvage rates, and long-term survival rates in early-stage ovarian germ cell tumors managed without adjuvant chemotherapy.

RADIATION

Chemotherapy has replaced radiation as the preferred adjuvant treatment for all types of malignant ovarian germ cell tumors. This transition was prompted primarily by the marked sensitivity of these tumors to either modality but the higher likelihood of retained ovarian function using chemotherapy (Mitchell, 1991). Occasional situations still may exist in which radiotherapy should be considered. However, the main role currently is palliation of a germ cell tumor that has demonstrated resistance to chemotherapy.

RELAPSE

At least four courses of BEP chemotherapy is the preferred treatment for recurrent ovarian germ cell tumors in women managed initially with surgery alone. Patients who achieved a sustained clinical remission of greater than 6 months after completing BEP or another platinum-based chemotherapy regimen may be treated again with BEP. Because their tumors generally are more responsive, these platinum-sensitive patients have a much better prognosis. However, women who do not achieve remission with BEP chemotherapy or relapse within a few months (<6) are considered platinum resistant. For these individuals, treatment options are limited. One option for this group is VAC (Gershenson, 1985). Other potentially active drugs include paclitaxel, gemcitabine, and oxaliplatin (Hinton, 2002; Kollmannsberger, 2006).

Second-look procedures with surgical debulking have a limited role because of the inherent chemosensitivity of these recurrent tumors. Chemorefractory immature teratomas are notable exceptions (Munkarah, 1994). Growth or persistence of a tumor after chemotherapy does not necessarily imply progression of malignancy, but these masses still should be resected (Geisler, 1994).

Prognosis

Malignant ovarian germ cell tumors have an excellent prognosis when managed appropriately (see Table 36-3) (Lai, 2005). Histologic cell type, surgical stage, and the amount of residual disease at initial surgery are the major variables affecting prognosis. However, of the germ cell tumor group, dysgerminomas have a better prognosis overall than the nondysgerminomatous types (Yilmaz, 2003).

Most women treated with fertility-sparing surgery, with or without chemotherapy, will resume normal menses and are able to conceive and bear children (Curtin, 1994; Mitchell, 1999). In addition, none of the reported studies has noted an increased rate of birth defects or spontaneous abortion in those treated with chemotherapy (Brewer, 1999; Low, 2000; Tangir, 2003; Zanetta, 2001).

Management during Pregnancy

Persistent adnexal masses are detected in 1 to 2 percent of all pregnancies. These neoplasms usually are seen during routine obstetric sonographic examination, but occasionally a dramatically elevated maternal serum AFP (MSAFP) level is the presenting sign of a malignant germ cell tumor (Horbelt, 1994; Montz, 1989). Mature cystic teratomas (dermoid cysts) comprise a third of tumors resected during pregnancy. In contrast, dysgerminomas account for only 1 to 2 percent of such neoplasms but still are the most common ovarian malignancy during pregnancy. Development of other germ cell tumors is rare (Shimizu, 2003).

Initial surgical management including surgical staging is the same as for the nonpregnant woman (Horbelt, 1994; Zhao, 2006). Fortunately, very few patients have advanced disease necessitating radical dissection for cytoreduction. The decision to administer chemotherapy during pregnancy is controversial. Malignant ovarian germ cell tumors have the propensity to grow rapidly, and delaying treatment until after delivery is potentially hazardous. Treatment with BEP appears to be safe during pregnancy, but some reports have speculated that fetal complications are possible (Elit, 1999; Horbelt, 1994). For this reason, some advocate postponing treatment until the puerperium (Shimizu, 2003). Unfortunately, there are no results from large studies to resolve this dilemma. At our institution, we delay BEP administration until the puerperium for completely resected dysgerminomas.

Nondysgerminomatous tumors (mainly yolk sac tumors and immature teratomas) and incompletely resected disease, however, warrant strong consideration of chemotherapy during pregnancy.

OVARIAN SEX CORDÂ€"STROMAL TUMORS

Sex cordâ€"stromal tumors (SCSTs) are a heterogeneous group of rare neoplasms that originate from the ovarian matrix. Cells within this matrix have the potential for hormone production, and nearly 90 percent of hormone-producing ovarian tumors are SCSTs. As a result, individuals with these tumors typically present with signs and symptoms of estrogen or androgen excess.

Surgical resection is the primary treatment, and SCSTs generally are confined to one ovary at the time of diagnosis. Moreover, most have an indolent growth pattern and low malignant potential. For these reasons, few patients ever require platinum-based chemotherapy. Although recurrent disease often responds poorly to treatment, patients may live for many years because of characteristically slow tumor progression.

The overall prognosis of ovarian SCSTs is excellentâ€"primarily due to early-stage disease at diagnosis and curative surgery. The scarcity of these tumors, however, limits the understanding of their natural history, treatment, and prognosis.

Epidemiology

SCSTs account for significantly fewer than 5 percent of ovarian malignancies and are the least common major subtype of ovarian cancer. The age-adjusted incidence rate is much lower (0.20 per 100,000 women) than that for epithelial ovarian carcinomas (15.48) and half of that for malignant germ cell tumors (0.41). These tumors are more than twice as likely to develop in black women for reasons that are unclear (Quirk, 2005).

In contrast with epithelial ovarian cancers or malignant germ cell tumors, ovarian SCSTs typically affect women of all ages. This range contains a unique bimodal distribution that reflects inherent tumor heterogeneity. For example, juvenile granulosa cell tumors, Sertoli-Leydig cell tumors, and sclerosing stromal tumors are found predominantly in prepubertal girls and women within the first three decades of life (Schneider, 2005). Adult granulosa cell tumors commonly develop in older women, with a peak incidence between 50 and 55 years (Miller, 1997).

The etiology of SCSTs is unknown, and there are no proven risk factors. Several reports in the past few of decades, however, have suggested an association with these tumors and use of combination oral contraceptive pills or ovulation-induction drugs (Willemsen, 1993; Centers for Disease Control and Prevention, 1987). These observations prompted concern that exposure of the gonad to persistently high levels of pituitary gonadotropins aid malignant transformation. More recently, however, this has been disputed by investigators who demonstrated a 40-percent decline in the incidence of SCSTs since the 1960s despite dramatic increases in the use of these drugs (Unkila-Kallio, 1998).

There is no known inherited predisposition for the development of these tumors, and familial cases are rare. However, ovarian SCSTs do develop in association with several defined hereditary disorders at a frequency that exceeds mere chance. Associated disorders include Ollier disease, which is characterized by multiple benign but disfiguring cartiliaginous neoplasms, and Peutz-Jeghers syndrome, which is characterized by intestinal hamartomatous polyps (Stevens, 2005).

Diagnosis

SIGNS AND SYMPTOMS

Isosexual pseudopuberty is the presenting sign in more than 80 precent of prepubertal girls ultimately diagnosed with an ovarian SCST (Kalfa, 2005). Adolescents often report secondary amenorrhea. As a result, these young individuals presenting with endocrinologic symptoms tend to be diagnosed at earlier stages. Abdominal pain and distention are other common complaints in this age group (Schneider, 2003a).

In adult women, menometrorrhagia and postmenopausal bleeding are the most common symptoms. In addition, mild hirsutism that rapidly progresses to frank virilization should prompt evaluation to exclude these tumors. The classic presentation is a postmenopausal woman with rapidly evolving stigmata of androgen excess and with a complex adnexal mass. Abdominal pain and a mass palpable by the patient herself are other telling signs and symptoms (Chan, 2005; Miller, 1997).

PHYSICAL EXAMINATION

The size of SCSTs is widely variable, but most women have a palpable abdominal or pelvic mass on examinationâ€"regardless of their age. A fluid wave and other physical findings suggestive of advanced disease, however, are rare.

LABORATORY TESTING

Elevated circulating levels of testosterone or androstendione or both are strongly suggestive of an ovarian SCST in a woman with signs and symptoms of virilization. Clinical hyperandrogenism is more likely to be polycystic ovarian syndrome or idiopathic, but serum testosterone levels greater than 200 g/dL or dehydroepiandrosterone sulfate (DHEAS) levels greater than 8,000 µg/L should strongly suggest the possibility of an androgen-secreting tumor (see Chap. 17, Dehydroepiandrosterone Sulfate) (Carmina, 2006). In most instances, tumor marker studies are not obtained preoperatively because the diagnosis of ovarian SCST often is not suspected. When the diagnosis is confirmed, the appropriate tumor markers may be determined during or following surgery (Table 36-4).

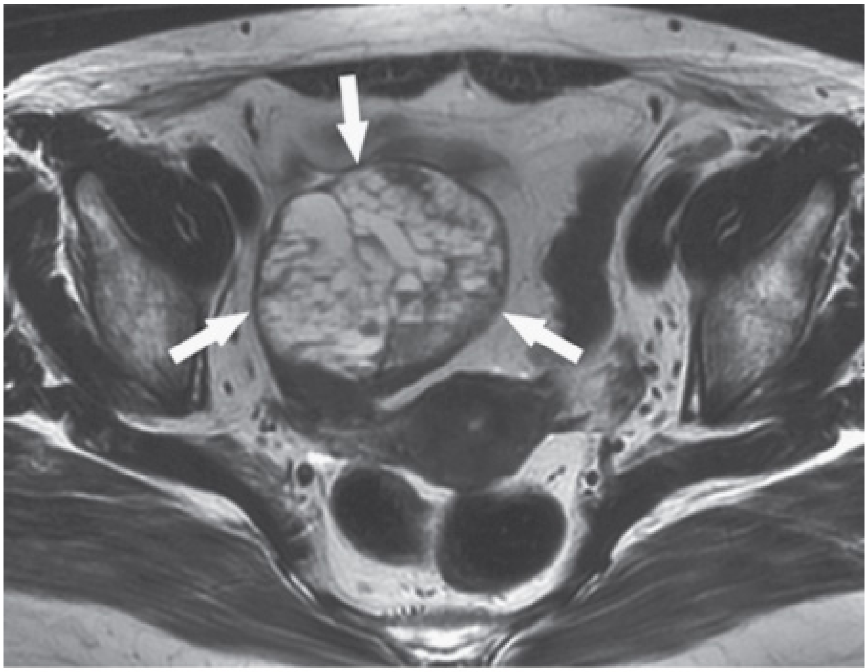
Table 36-4 Tumor Markers for Ovarian Sex Cord-Stromal Tumors with Malignant Potential

Granulosa cell tumors (adult and juvenile)	Inhibin A and B, estradiol (not as reliable)
Sertoliâ€"Leydig cell tumors	Inhibin A and B, alpha-fetoprotein (occasionally)
Sex cord tumor with annular tubules	Inhibin A and B
Steroid cell tumors not otherwise specified	Steroid hormones elevated pretreatment

IMAGING

The gross appearances of SCSTs range from large multicystic masses to small solid massesâ€"effectively precluding a specific radiologic diagnosis. Granulosa cell tumors often demonstrate semisolid features sonographically but are not reliably discernible from epithelial tumors (Sharony, 2001). In addition, the endometrium may be thickened from increased tumor estrogen production. Although CT scanning or MR imaging has been used to clarify indeterminant sonograms, there is no definitive radiologic study to diagnose these tumors (Fig. 36-4) (Jung, 2005).

FIGURE 36-4



Computed tomographic (CT) scan of a granulosa cell tumor. *(From Jung, 2005, with permission.)*

DIAGNOSTIC PROCEDURES

Patients with an ovarian mass suspicious for malignancy based on clinical and sonographic findings require surgical resection for definitive tissue diagnosis, staging, and treatment. Sonographically or CT-guided percutaneous biopsy has no role. Moreover, diagnostic laparoscopy or laparotomy with visual assessment of the adnexal mass alone is inadequate. Therefore, excision and pathologic evaluation are necessary.

Following removal, ovarian SCSTs usually can be distinguished histologically from germ cell tumors, epithelial ovarian cancers, or other spindle cell neoplasms by immunostaining for inhibin (Cathro, 2005; Schneider, 2005).

Role of the Generalist

Preoperatively, patients with a potentially malignant ovarian SCST should be referred to a gynecologic oncologist for evaluation. Most ovarian SCSTs, however, are diagnosed by generalists in obstetrics and gynecology following resection of a seemingly benign but complex mass in a woman with a CA125 level that is typically normal, if known beforehand. The initial surgery often is performed in a community-based hospital and without adequate staging. In this setting, prior to referral, histologic results should be reviewed and confirmed by an experienced pathologist. Following referral to a gynecologic oncologist, surgical staging via laparotomy or laparoscopy may be indicated.

Pathology

CLASSIFICATION

Ovarian SCSTs arise from sex cord and mesenchymal cells of the embryonic gonad (see Chap. 18, Gonadal Differentiation). Granulosa and Sertoli cells develop from the sex cords and thus from the coelomic epithelium. In contrast, theca cells, Leydig cells, and fibroblasts are derived from the mesenchyme (future stroma). This primitive gonadal stroma possesses sexual bipotentiality. Therefore, developing tumors may be composed of a male-directed cell type (Sertoli or Leydig cell) or a female-directed cell type (granulosa or theca cells). Although distinct categories of SCSTs have been defined, mixed tumors are relatively common (Table 36-5). For example, ovarian granulosa cell tumors may have admixed Sertoli components. Similarly, tumors that are

predominantly Sertoli or Sertoli-Leydig cells may contain minor granulosa elements. These mixed tumors are believed to arise from a common lineage with variable differentiation and do not represent two concurrent separate entities (McKenna, 2005; Vang, 2004).

Table 36-5 World Health Organization Classification of Ovarian Sex Cordâ€"Stromal Tumors
Granulosa-stromal cell tumors
Granulosa cell tumor
Adult type
Juvenile type
Thecoma-fibroma group
Thecoma
Fibroma/fibrosarcoma
Sclerosing stromal tumor
Sertoliâ€"stromal cell tumors
Sertoli cell tumor
Sertoliâ€"Leydig cell tumor
Sex cord tumor with annular tubules
Steroid cell tumors
Stromal luteoma
Leydig cell tumor
Steroid cell tumor not otherwise specified
Unclassified
Gynandroblastoma

HISTOLOGIC GRADING

Ovarian granulosa cell tumors are universally considered to have malignant potential, but most other SCST subtypes do not have definitive criteria for clearly defining benign and malignant. Attempts to grade these tumors using nuclear characteristics or mitotic activity counts have produced inconsistent results (Chen, 2003).

PATTERNS OF GROWTH AND SPREAD

The natural history of SCSTs in general differs greatly from that of epithelial ovarian carcinomas. For example, most of these tumors have low malignant potential. They are typically unilateral and remain localized, retain hormone-secreting functions, and infrequently relapse. Recurrences tend to be late and usually develop in the abdomen or pelvis. Bone metastases are extremely rare (Dubuc-Lissoir, 2001).

Granulosa Cell Tumors

Seventy percent of ovarian SCSTs are granulosa cell tumors. These tumors are formed by cells believed to arise from those surrounding the germinal cells within ovarian follicles. There are two clinically and histologically distinct types: the adult form, which comprises 95 percent of cases, and the juvenile type, comprising 5 percent.

ADULT GRANULOSA CELL TUMORS

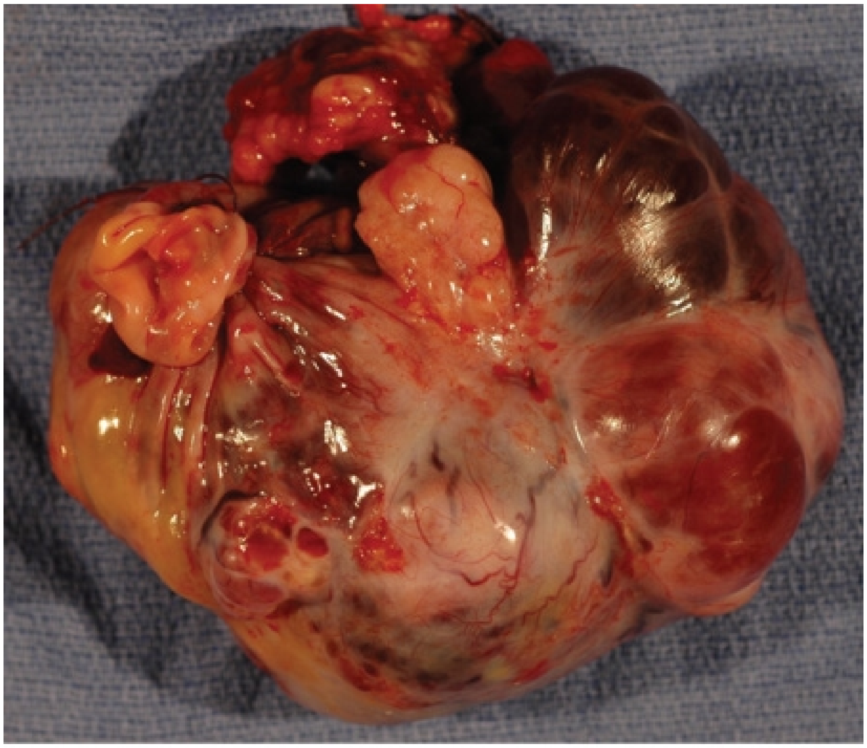
Clinical Findings

Most women with an adult granulosa cell tumor are diagnosed after age 30, with the average age being 52 years. Menometrorrhagia and postmenopausal bleeding are common signs and reflect a prolonged exposure of the endometrium to estrogen (Miller, 1997). Related to this estrogen excess, coexisting pathologyâ€”such as endometrial hyperplasia or adenocarcinomaâ€”has been found in one quarter of patients with adult granulosa cell tumor. Similarly, breast enlargement and tenderness are common associated complaints, and secondary amenorrhea has been reported (Kurihara, 2004). Alternatively, symptoms may stem from the mass of the ovary rather than from hormones produced. An enlarging and potentially hemorrhagic tumor may cause abdominal pain and distention. Acute pelvic pain may suggest adnexal torsion, or tumor rupture with hemoperitoneum can mimic ectopic pregnancy.

During surgery, if an adult granulosa cell tumor is confirmed, tumor markers may be requested. Of these, inhibin A, inhibin B, and serum estradiol levels are most valuable. Inhibins have been demonstrated to be elevated months before clinical detection of disease and therefore, are considered more reliable for postoperative surveillance (Boggess, 1997; Lappohn, 1989). The diagnostic value of this marker, however, sometimes may be hampered by its physiologically broad normal range (Schneider, 2005). Estradiol has limited use in surveillance, particularly in a younger woman wishing to preserve fertility and having the contralateral ovary left in situ.

Grossly, adult granulosa cell tumors are large, multicystic, and often exceed 10 to 15 cm in diameter (Fig. 36-5). The surface is frequently edematous and unusually adherent to other pelvic organs. For this reason, more extensive dissection typically is required than for epithelial ovarian cancers or malignant germ cell tumors. During excision, inadvertent rupture and intraoperative bleeding from the tumor itself also are common.

FIGURE 36-5

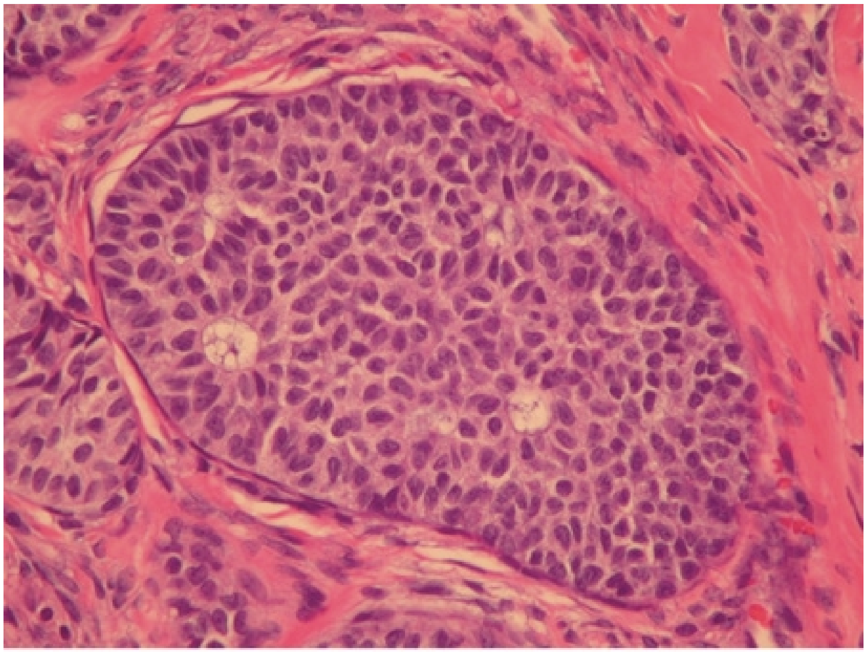


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

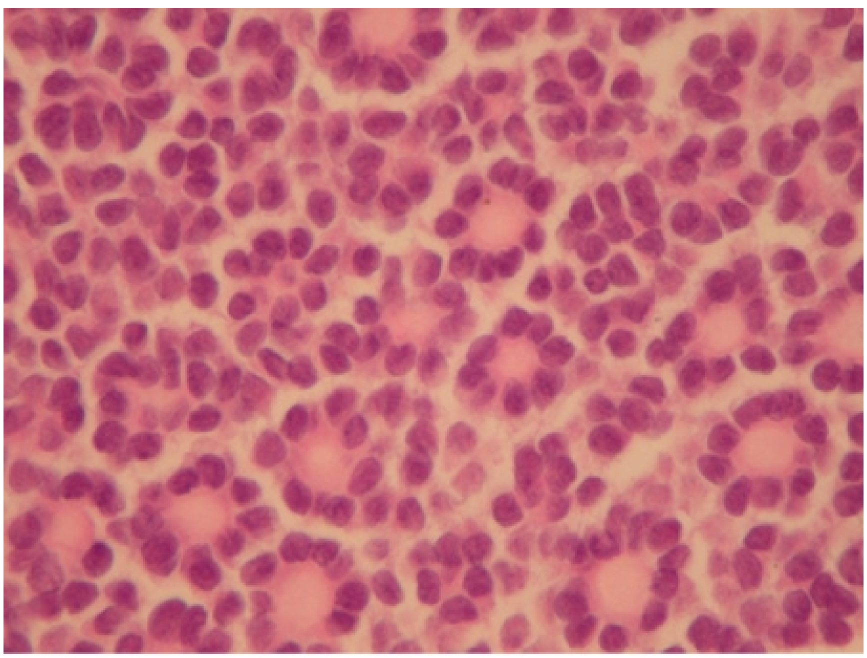
Adult granulosa cell tumor. *(Courtesy of Dr. Raheela Ashfaq.)*

The interior of the tumor typically has a variable solid and cystic appearance with hemorrhagic areas. Microscopic examination shows predominately granulosa cells with pale, grooved, "coffee bean" nuclei. The characteristic microscopic feature is the *Call-Exner body* â€”a rosette arrangement of cells around an eosinophilic fluid space (Fig. 36-6).

FIGURE 36-6



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Adult granulosa cell tumor. Call-Exner bodies are identified by their rosette appearance. *(Courtesy of Dr. Raheela Ashfaq.)*

Prognosis

Adult granulosa cell tumors are low-grade malignancies that typically demonstrate indolent growth. Ninety-five percent are unilateral, and 80 to 90 percent are stage I at diagnosis (Table 36-6). The 5-year survival for patients with stage I disease is 85 to

95 percent (Lauszus, 2001; Malmstrom, 1994; Miller, 1997). However, 15 to 25 percent of stage I tumors eventually will relapse. The median time to recurrence is 6 years but may be several decades (East, 2005). Fortunately, these indolent tumors usually progress slowly thereafter, and the median length of survival after relapse is another 6 years. Advanced tumor stage and residual disease are poor prognostic factors (Al Badawi, 2002; Sehouli, 2004). Stage IIâ€“IV tumors have a 5-year survival of 30 to 50 percent (Malmstrom, 1994; Miller, 1997; Piura, 1994). Cellular atypia and mitotic count may help in determining the prognosis but are difficult to quantify reproducibly (Miller, 2001).

Table 36-6 Stage and Survival of Common Ovarian Sex Cordâ€“Stromal Tumors

	Adult Granulosa Cell	**Sertoliâ€“Leydig Cell**
Stage at diagnosis		
I	80â€“90%	97%
IIâ€“IV	10â€“20%	2â€“3%
Five-year survival		
Stage I	85â€“95%	90â€“95%
Stage IIâ€“IV	30â€“50%	10â€“20%

Sources for survival figures are referenced within the text.

JUVENILE GRANULOSA CELL TUMORS

Clinical Findings

These rare neoplasms develop primarily in children and young adults, and half are diagnosed before puberty. The mean age at diagnosis is 13 years, but patients range from newborn to 67 years (Young, 1984). Juvenile granulosa cell tumors sometimes are associated with Ollier disease and Maffucci's syndrome (endochondromas and hemangiomas) (Young, 1984; Yuan, 2004).

In affected females, estrogen, progesterone, and testosterone levels may be elevated with suppression of gonadotropins. As a result, menstrual irregularities and amenorrhea are common. Prepubertal girls typically display isosexual peripheral precocious puberty, which is characterized by breast enlargement and development of pubic hair, vaginal secretions, and other secondary sexual characteristics (see Chap. 14, Precocious Puberty). These tumors infrequently secrete androgens, but in such cases, they may induce virilization. Despite these endocrinologic signs, a delayed diagnosis of juvenile granulosa cell tumors in pre- and postpubertal girls is common and associated with a high risk of peritoneal tumor spread (Kalfa, 2005).

In addition to hormonal effects, individuals may display tumor effects. For example, older patients usually seek medical attention for abdominal pain or swelling. Preoperative rupture with resulting hemoperitoneum may create acute abdominal symptoms in 5 percent of patients. Additionally, ascites is present in 10 percent (Young, 1984).

Juvenile granulosa cell tumors are grossly similar to the adult-type tumor with variable solid and cystic components. They can attain significant size, and the average diameter is 12 cm. Microscopically, cytologic features that distinguish these tumors from the adult type are their rounded, hyperchromatic nuclei without "coffee-bean" grooves. Call-Exner bodies are rare, but often there is a theca cell component (Young, 1984).

Prognosis

Prognosis is excellent, and the 5-year survival rate is 95 percent. Similar to adult-type tumors, 95 percent of juvenile granulosa cell tumors are unilateral and stage I at diagnosis (Young, 1984). However, the juvenile type is more aggressive in advanced stages, and the time to relapse and death is much shorter. Recurrences typically develop within 3 years. Later recurrences are unusual (Frausto, 2004).

Thecoma-Fibroma Group

THECOMAS

Thecomas are relatively common SCSTs that are unique because they typically develop in postmenopausal women in their mid-60s and develop infrequently before age 30. These solid tumors are among the most hormonally active of the SCSTs and usually produce excess estrogen. As a result, primary signs and symptoms are abnormal vaginal bleeding or pelvic mass or both. Many women also present with concurrent endometrial hyperplasia or adenocarcinoma (Aboud, 1997). These tumors are composed of lipid-laden stromal cells that are occasionally luteinized. Half these luteinized thecomas are either hormonally inactive or androgenic with the potential for inducing masculinization.

Thecomas are solid tumors that resemble the theca cells that normally surround the ovarian follicles (Chen, 2003). Because of this texture, these tumors appear sonographically as solid adnexal masses and may mimic extrauterine leiomyomas.

Bilateral ovarian involvement and extraovarian spread are rare. Fortunately, ovarian thecomas are clinically benign, and surgical resection is curative.

FIBROMAS/FIBROSARCOMAS

Fibromas are relatively common, hormonally inactive SCST variants. These solid, generally benign ovarian neoplasms arise from the spindled stromal cells that form collagen. Fibromas can produce ascites, resulting in a clinical picture (Meigs syndrome) suggestive of epithelial ovarian cancer (see Chap. 9, Other Clinical Manifestations). (Siddiqui, 1995). Ten percent will demonstrate increased cellularity and varying degrees of pleomorphorism and mitotic activity that indicate a tumor better characterized as having low malignant potential. Fibrosarcomas are rare, highly malignant tumors that have even more dramatic histologic features.

Sclerosing Stromal Tumors

These tumors are rare and account for less than 5 percent of SCSTs. The average patient age is 21 years, and 80 percent develop before age 30. Sclerosing stromal tumors are clinically benign and typically unilateral. Menstrual irregularities and pelvic pain are both common symptoms (Marelli, 1998). Ascites is seldom encountered (unlike fibromas), and sclerosing stromal tumors are hormonally inactive (unlike thecomas). Tumor size ranges from microscopic to 20 cm. Histologically, the presence of pseudolobulation of cellular areas separated by edematous connective tissue, increased vascularity, and prominent areas of sclerosis are distinguishing features.

Sertoliâ€“Stromal Cell Tumors

SERTOLI CELL TUMORS

Ovarian Sertoli cell tumors are rare and account for less than 5 percent of all SCSTs. The mean patient age at diagnosis is 30 years, but ages range from 2 to 76 years. One quarter of patients present with estrogenic or androgenic manifestations, but most tumors are clinically nonfunctional.

Sertoli cell tumors typically are unilateral, solid, yellow, and measure 4 to 12 cm. Derived from the cell type that gives rise to the seminiferous tubules, these tumor cells often organize into histologically characteristic tubules (Young, 2005). Sertoli cell tumors, however, also may mimic many different tumors, and immunostaining in these cases is invaluable to confirm the diagnosis.

More than 80 percent are stage I at diagnosis, and most are clinically benign. Moderate cytologic atypia, brisk mitotic activity, and tumor cell necrosis are indicators of greater malignant potential. These findings are found in 10 percent of individuals with stage I disease and in most of those with stage IIâ€“IV tumors. The risk of recurrence is higher when these features are identified (Oliva, 2005).

SERTOLI-LEYDIG CELL TUMORS

Sertoliâ€“Leydig cell tumors comprise only 5 to 10 percent of ovarian SCSTs. Their incidence mirrors that of Sertoli cell tumors, and the average age is 25 years. Although Sertoliâ€“Leydig cell tumors have been identified in children and postmenopausal females, more than 90 percent develop during the reproductive years.

These tumors frequently produce sex steroid hormones, most commonly androgens. As a result, frank virilization develops in a third of women, and another 10 percent have clinical manifestations of androgen excess characterized by hirsutism, temporal balding, deepening of the voice, and clitoral enlargement (Young, 1985). Menstrual disorders are also common. Accordingly, Sertoliâ€"Leydig cell tumors should be suspected preoperatively in a patient with a unilaterally palpable adnexal mass and androgenic manifestations. For these women, an elevated serum testosterone:androstenedione ratio further suggests the diagnosis.

Although these hormonal effects develop frequently, half of patients will have nonspecific abdominal mass symptoms as their only presenting complaint. Associated ascites is uncommon (Outwater, 2000). Thyroid abnormalities also coexist with Sertoliâ€"Leydig cell tumors at a frequency that exceeds mere chance.

These tumors tend to be large at the time of excision, with an average diameter of 13 cm, but ranges from 1 to 50 cm have been reported. In most cases, Sertoliâ€"Leydig cell tumors appear yellow and lobulated. Tumors can be solid, partially cystic, or completely cystic, and they may or may not have polypoid or vesicular structures in their interior. Microscopically, these morphologically diverse tumors contain cells resembling epithelial and stromal testicular cells in varying proportions. The five subtypes of differentiation (well, intermediate, poor, retiform, and heterologous) have considerable overlap. Well-differentiated tumors are all clinically benign (Chen, 2003; Young, 2005).

Overall, 15 to 20 percent of Sertoliâ€"Leydig cell tumors are clinically malignant. Prognosis depends predominantly on the stage and degree of tumor differentiation in these malignant variants. For example, Young and Scully (1985) performed a clinicopathological analysis of 207 patients and identified stage I disease in 97 percent. The 5-year survival for patients with stage I disease exceeds 90 percent (Zaloudek, 1984). Malignant features were observed in approximately 10 percent of tumors with intermediate differentiation and 60 percent of poorly differentiated tumors. Retiform and heterologous elements are seen only in intermediate or poorly differentiated Sertoliâ€"Leydig cell tumors and typically are associated with poorer prognosis. Overall, the 2 to 3 percent of patients with stage IIâ€"IV disease have a dismal prognosis (Young, 1985).

Sex Cord Tumors with Annular Tubules

Sex cord tumors with annular tubules account for 5 percent of SCSTs and are characterized by ring-shaped tubules and distinctive cellular elements that are histologically intermediate between Sertoli cell and granulosa cell tumors. There are two clinically distinct types. First, one third are clinically benign and develop in patients with Peutz-Jeghers syndrome (PJS). These tumors are typically small, multifocal, calcified, bilateral, and are diagnosed incidentally. Fifteen percent of PJS-associated patients also will develop adenoma malignum of the cervix, which is a rare and extremely well-differentiated adenocarcinoma. In contrast, two thirds of tumors are not associated with PJS. These tumors are usually larger, unilateral, symptomatic, and carry a clinical malignancy rate of 15 to 20 percent (Young, 1982).

Steroid Cell Tumors

Fewer than 5 percent of SCSTs are steroid cell tumors. The average age at diagnosis is the mid-20s, but patients can present at virtually any age. These tumors are composed entirely or predominantly of cells that resemble steroid hormoneâ€"secreting cells and are categorized according to the histologic composition of these cells. *Stromal luteomas* are clinically benign tumors that, by definition, lie completely within the ovarian stroma. They are usually seen in postmenopausal women. Estrogenic effects are common, but occasional individuals have androgenic manifestations. *Leydig cell tumors* are also benign and typically seen in postmenopausal women. They are distinguished microscopically by crystals of Reinke within the cytoplasm. Leydig cells secrete testosterone, and these tumors usually are associated with androgenic effects. *Steroid cell tumors not otherwise specified* (NOS) are the most common subtype within this group and typically present in younger reproductive-aged women. Some of these may represent large stromal luteomas that have grown to reach the ovarian surface or Leydig cell tumors in which Reinke crystals cannot be identified. These tumors typically are associated with androgenic excess, but estrogenic or cortisol overproduction (i.e., Cushing syndrome) also has been reported. A third of steroid cell tumors NOS are clinically malignant and have a dismal prognosis (Oliva, 2005).

Unclassified Sex Cordâ€"Stromal Tumors

Unclassified tumors account for 5 percent of SCSTs and have no clearly predominant pattern of testicular (Sertoli cells) or ovarian

(granulosa cells) differentiation. These ill-defined tumors are especially common during pregnancy owing to alterations in their usual clinical and pathologic features (Young, 2005). They may be estrogenic, androgenic, or nonfunctional. The prognosis is similar to that of granulosa cell tumors and Sertoliâ€"Leydig cell tumors of similar degrees of differentiation.

Gynandroblastomas

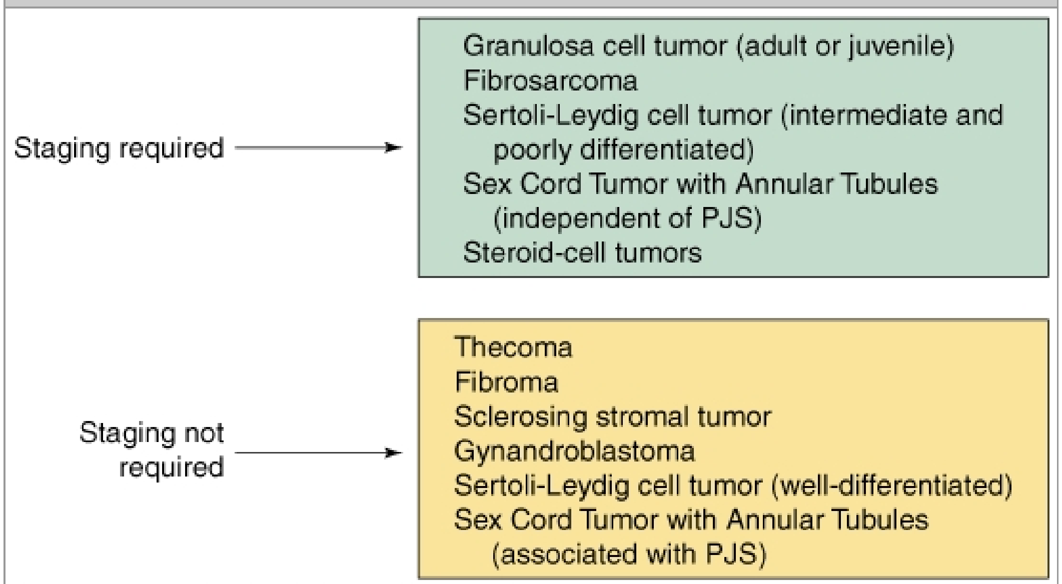
Gynandroblastomas are the rarest type of ovarian SCST. Women present at a mean age of 30 years and typically have menstrual irregularities or evidence of hormonal excess. The tumors are characterized by intermingled granulosa cells and tubules of Sertoli cells. Theca or Leydig cells or both also may be present in varying degrees. Gynandroblastomas have low malignant potential, and only one death has been reported (Martin-Jimenez, 1994).

Treatment

SURGERY

The mainstay of treatment for patients with an ovarian SCST is surgical resection. The goals of surgery are to establish a definitive tissue diagnosis, determine the extent of disease by appropriate ovarian cancer staging procedures, and remove all grossly visible disease (see Chap. 35, Surgical Approach to Cytoreductive Surgery). Staging laparotomy or laparoscopy is essential to determine the extent of disease and the need for adjuvant therapy in most individuals with potentially malignant SCST subtypes (Fig. 36-7) (Chan, 2005). Moreover, in planning surgery, clinicians should consider the patient's age and desire for future fertility. Hysterectomy with BSO is performed for those who have completed childbearing, whereas fertility-sparing USO with preservation of the uterus may be appropriate in the absence of obvious disease spread to these organs (Zanagnolo, 2004). Endometrial sampling should be performed especially when fertility-sparing surgery is planned in women with granulosa cell tumors or thecomas because many of these patients will have coexisting hyperplasia or adenocarcinoma that may affect the decision for hysterectomy.

FIGURE 36-7



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Staging of sex cordâ€"stromal tumors. PJS = Peutz-Jeghers syndrome.

Minimally invasive laparoscopic surgery has a variety of relevant applications. For some, the diagnosis of SCST may not be discovered until the mass is removed laparoscopically and sent for frozen section evaluation. Laparoscopic surgical staging then can proceed. When the diagnosis is not made until the final pathology report is confirmed postoperatively, laparoscopic staging may be proposed to determine whether metastatic disease is present while reducing the morbidity of another operation (Kriplani, 2001).

Surgical removal of hormone-producing SCSTs results in an immediate drop in elevated preoperative sex steroid hormone levels. Physical manifestations of these elevated levels, however, resolve partially or completely more gradually.

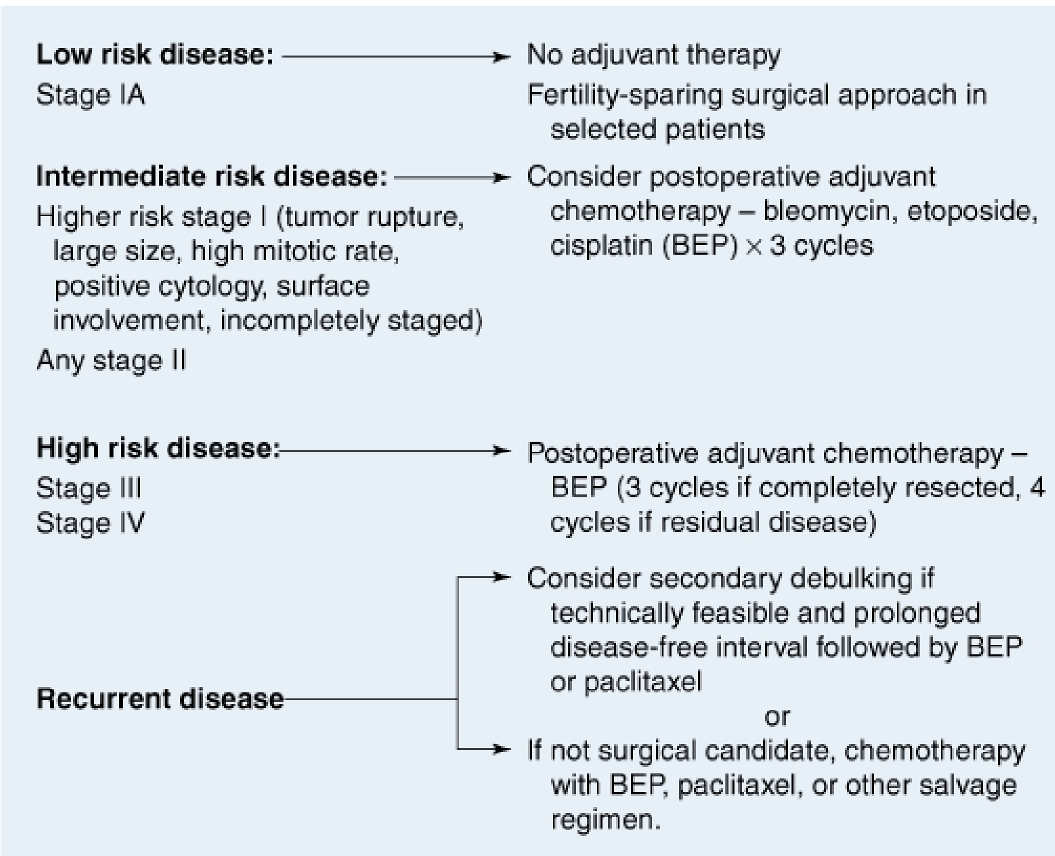
SURVEILLANCE

In general, women with stage I ovarian SCSTs have an excellent prognosis following surgery alone and usually can be followed at regular intervals without the need for further treatment (Schneider, 2003a). Surveillance includes a general physical and pelvic examination, serum marker testing, and imaging tests as clinically indicated.

CHEMOTHERAPY

The decision to administer postoperative therapy depends on a variety of factors (Fig. 36-8). Although typically treated solely with surgery, malignant stage I ovarian SCSTs may require adjuvant chemotherapy when large tumor size, high mitotic index, capsular excrescences, tumor rupture, incomplete staging, or equivocal pathology results are noted. Women with one or more of these suspicious features are thought to be at higher risk of relapse and should be considered for platinum-based chemotherapy (Schneider, 2003b). In addition, stage IIâ€“IV disease warrants postoperative treatment. In general, SCSTs display less sensitivity to chemotherapy than other ovarian malignancies, but most women at high risk for disease progression can be treated successfully with adjuvant cisplatin-based chemotherapy (Schneider, 2005).

FIGURE 36-8



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Postoperative treatment of sex cordâ€“stromal tumors.

The 5-day bleomycin, etoposide, and cisplatin (BEP) regimen is the most widely used first-line chemotherapy combination (Gershenson, 1996; Homesley, 1999). For those with completely resected disease, three courses given every 3 weeks are sufficient.

Four cycles are recommended for patients with incompletely resected tumor (Homesley, 1999). In addition to BEP, taxanes have demonstrated activity against ovarian SCSTs, and combination paclitaxel and carboplatin chemotherapy has shown promising results (Brown, 2004, 2005). Unfortunately, the relative rarity of women who have ovarian SCST and receive chemotherapy limits the ability to conduct randomized studies.

RADIATION

Postoperative radiation therapy currently has a limited role in the management of ovarian SCSTs. There is some evidence indicating a prolonged survival in at least some women with newly diagnosed disease who received whole abdominal radiotherapy (Wolf, 1999). However, chemotherapy is usually the primary postoperative treatment because it is generally better tolerated, more widely accessible, and easier to administer. Radiation is best reserved for palliation of local symptoms (Dubuc-Lissoir, 2001).

RELAPSE

The management of recurrent ovarian SCST depends on the clinical circumstances. Secondary surgical debulking should be strongly considered because of the indolent growth pattern, the typically long disease-free interval after initial treatment, and the inherent insensitivity to chemotherapy (Crew, 2005; Powell, 2001). Platinum-based combination chemotherapy is the primary treatment chosen for recurrent disease, with or without surgical debulking (Uygun, 2003). Of available regimens, BEP is administered most frequently because it has the highest known response rate (Homesley, 1999). Paclitaxel is another promising agent that is currently being evaluated in a phase II Gynecologic Oncology Group trial (protocol 187) and warrants further investigation when combined with platinum (Brown, 2005).

There is no standard treatment for women who have progressive disease despite aggressive surgery and platinum-based chemotherapy. The vincristine, actinomycin D, and cyclophosphamide (VAC) regimen has limited activity (Ayhan, 1996; Zanagnolo, 2004). However, hormone therapy may be useful and minimally toxic in women with chemoresistant tumors (Hardy, 2005). Medroxyprogresterone acetate and the GnRH agonist leuoprolide acetate each have demonstrated activity in halting the growth of recurrent ovarian SCSTs (Fishman, 1996; Homesley, 1999). GnRH antagonists, however, may not be as effective (Ameryckx, 2005). In addition to traditional drugs, novel agents have been synthesized that bind to specific ovarian SCST tumor receptors and lead to cell death. These are still under investigation in animal models and are not yet available clinically (Bodek, 2005).

Prognosis

In general, ovarian SCSTs portend a much better prognosis than epithelial ovarian carcinomas chiefly because most women with SCSTs are diagnosed with stage I disease. Stage IIâ€"IV tumors are rare, but women with these cancers have a poor prognosis similar to their epithelial counterparts. Of the clinical factors affecting prognosis, surgical stage is the most important (Zanagnolo, 2004). Chan and colleagues (2005) performed a multivariate analysis of 83 women with SCSTs and concluded that age younger than 40 years, smaller tumor size, and complete tumor removal also were independent predictors of improved survival.

Management during Pregnancy

Ovarian SCSTs are detected rarely during pregnancy (Okada, 2004). In a California population-based study of more than 4 million obstetric patients, one granulosa cell tumor was diagnosed among 202 women with an ovarian malignancy (Leiserowitz, 2006). Granulosa cell tumors are the most common SCST, but only 10 percent are diagnosed during pregnancy (Hasiakos, 2006). A third of pregnant women with SCSTs are diagnosed incidentally at cesarean delivery, a third have abdominal pain or swelling, and the remainder may present with hemoperitoneum, virilization, or vaginal bleeding (Young, 1984).

Surgical management should be the same as for the nonpregnant woman. For most, conservative management with USO and surgical staging is the primary procedure, but hysterectomy and BSO may be indicated in selected circumstances (Young, 1984). Postoperative chemotherapy typically is withheld at our institution until after delivery because SCSTs have an indolent growth pattern.

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GESTATIONAL TROPHOBLASTIC DISEASE: INTRODUCTION

Gestational trophoblastic disease (GTD) refers to a spectrum of interrelated but histologically distinct tumors originating from the placenta (Table 37-1). These diseases are characterized by a reliable tumor marker (β-subunit of human chorionic gonadotropin [β-hCG]) and have varying tendencies toward local invasion and spread.

Table 37-1 Modified World Health Organization Classification of Gestational Trophoblastic Disease

Molar lesions
Hydatidiform mole
Complete
Partial
Invasive mole
Nonmolar lesions
Choriocarcinoma
Placental site trophoblastic tumor
Epithelioid trophoblastic tumor

Modified from le-Ming, 2002, with permission.

Gestational trophoblastic neoplasia (GTN) refers to the subset of gestational trophoblastic disease that develops malignant sequelae. These tumors require formal staging and typically respond favorably to chemotherapy. Most commonly, GTN develops after a molar pregnancy but may follow any gestation.

The prognosis for most cases of GTN is excellent, and patients are cured routinely even in the presence of widespread metastases. The outlook for preservation of fertility and for successful subsequent pregnancy outcomes is equally bright (Schorge, 2000). Accordingly, although gestational trophoblastic disease is uncommon, because the opportunity for cure is great, clinicians should be familiar with its presentation, diagnosis, and management.

EPIDEMIOLOGY AND RISK FACTORS

Incidence

The incidence of gestational trophoblastic disease has remained fairly constant at approximately 1 to 2 per 1,000 deliveries in the United States and Europe (Drake, 2006; Loukovaara, 2005; Smith, 2003). A similar frequency has been observed in South Africa and Turkey (Moodley, 2003; Ozalp, 2003). Although higher incidence rates have been reported in parts of Asia, this may have largely reflected discrepancies between population-based and hospital-based data collection. For example, a recent South Korean population-based study noted a drop in the incidence from 40 per 1,000 deliveries to 2 per 1,000 that was coincident with refinement in disease terminology and classification (Kim, 2004). Similarly, hospital-based studies in Japan and Singapore have shown a decreased incidence approaching that in the United States and Europe (Chong, 1999; Matsui, 2003). Some ethnic groups, however, appear to be at higher risk of developing gestational trophoblastic disease. Hispanics and Native Americans living in the United States reportedly have an increased incidence, as do certain population groups living in Southeast Asia (Drake, 2006; Smith, 2003; Tham 2003).

Maternal Age

Maternal age at the upper and lower extremes has been found to carry a higher risk of gestational trophoblastic disease (Loukovaara, 2005; Tham, 2003). More specifically, teenage women and those aged 36 to 40 years have approximately double the risk. Patients older than 40 years of age have a 7.5-fold higher risk, and the association is most pronounced among women at least 45 years of age (Parazzini, 1991; Sebire, 2002a). One explanation may relate to ova from older women having higher rates of abnormal fertilization (Schorge, 2000). Similarly, older paternal age also has been associated with increased risk (La Vecchia, 1984; Parazzini, 1986).

Obstetric History

In addition to age, a history of prior unsuccessful pregnancies increases the risk of gestational trophoblastic disease. For example, previous spontaneous abortion at least doubles the risk of molar pregnancy (Parazzini, 1991). Moreover, a personal history of gestational trophoblastic disease increases the risk of developing a molar gestation in a subsequent pregnancy by at least 10-fold (Parazzini, 1991; Sebire, 2003). The frequency in a subsequent conception is approximately 1 to 2 percent, and most cases mirror the same type of mole as the preceding pregnancy (Berkowitz, 1994). Furthermore, following two episodes of molar pregnancy, 23 percent of later conceptions result in another molar gestation (Berkowitz, 1998). For this reason, women with a prior history of gestational trophoblastic disease should undergo first-trimester sonographic examination in subsequent pregnancies. Familial molar pregnancies, however, are exceedingly rare (Fallahian, 2003).

Other Factors

In several case-control studies, combination oral contraceptive (COC) pill use has been associated with an increased risk of gestational trophoblastic disease. Specifically, prior COC pill use approximately doubles the risk, and a longer duration of use also seems to correlate positively with risk (Palmer, 1999; Parazzini, 2002). Moreover, women who used combination oral contraceptive pills during the cycle in which they became pregnant appear to have a fourfold higher risk (Palmer, 1999). Many of these associations, however, are weak and could be explained by confounding factors other than causality (Parazzini, 2002).

Certain epidemiologic characteristics appear to differ markedly between complete and partial moles. For example, vitamin A deficiency and low dietary intake of carotene are associated with an increased risk of only complete moles (Berkowitz, 1985, 1995; Parazzini, 1988a). Partial moles have been linked to higher educational levels, smoking, irregular menstrual cycles, and obstetric histories in which only male infants are among the prior live births (Berkowitz, 1995; Parazzini, 1986).

HYDATIDIFORM MOLE (MOLAR PREGNANCY)

Hydatidiform moles are abnormal pregnancies characterized histologically by aberrant changes within the placenta. Specifically, the chorionic villi in these placentas show varying degrees of trophoblastic proliferation and edema of the villous stroma. Based on the degree and extent of these tissue changes, hydatidiform moles are categorized as either *complete hydatidiform moles* or *partial hydatidiform moles* (Table 37-2). Cytogenetic studies have shown that chromosomal abnormalities play an integral role in the

development of hydatidiform moles (Lage, 1992). Overall survival from these potentially malignant conditions has been virtually 100 percent for the past few decades (Lurain, 1983).

Table 37-2 Features of Complete and Partial Hydatidiform Moles

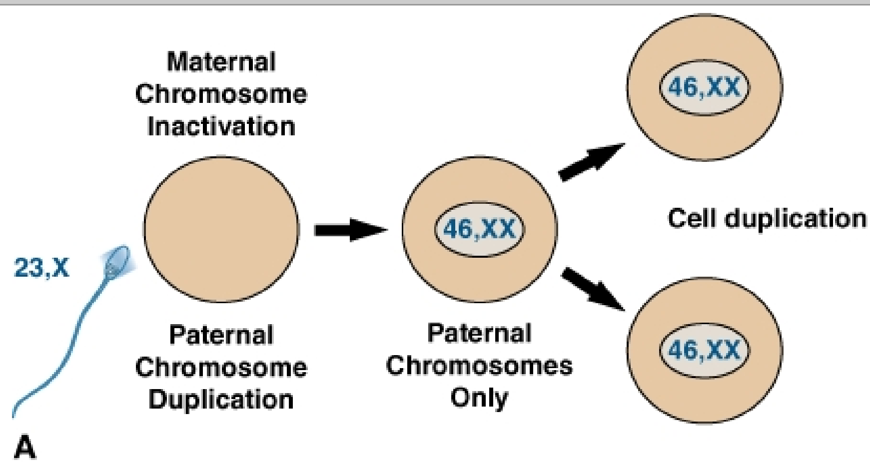
Feature	Complete Mole	Partial Mole
Karyotype	46,XX or 46,XY	69,XXX or 69,XXY
Pathology		
Fetus/embryo	Absent	Present
Villous edema	Diffuse	Focal
Trophoblastic proliferation	Variable, may be marked	Focal and minimal
p57Kip2 immunostaining	Negative	Positive
Clinical presentation		
Typical Diagnosis	Molar gestation	Missed abortion
Postmolar malignant sequelae	15â€"20%	2â€"4%

Complete Hydatidiform Mole

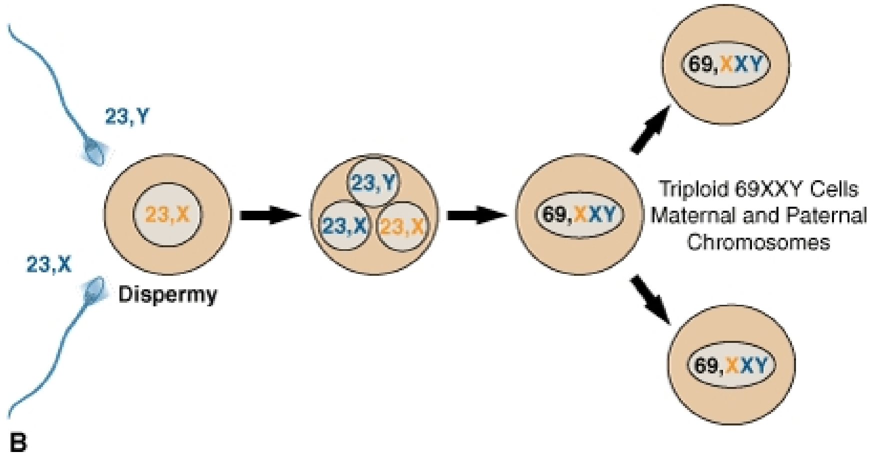
KARYOTYPE AND HISTOLOGY

Classically, these molar pregnancies differ from partial moles with regard to their karyotype, their histologic appearance, and their clinical presentation. Complete moles typically have a complete diploid karyotype, and 85 percent of these are 46,XX. The chromosomes, however, in these pregnancies are entirely of paternal origin. In a process termed *androgenesis,* the ovum is fertilized by a haploid sperm, which then duplicates its own chromosomes after meiosis (Fig. 37-1) (Fan, 2002; Kajii, 1977). Although most of these moles are 46,XX, dispermic fertilization of a single ovum can produce a 46,XY karyotype (Lawler, 1987).

FIGURE 37-1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

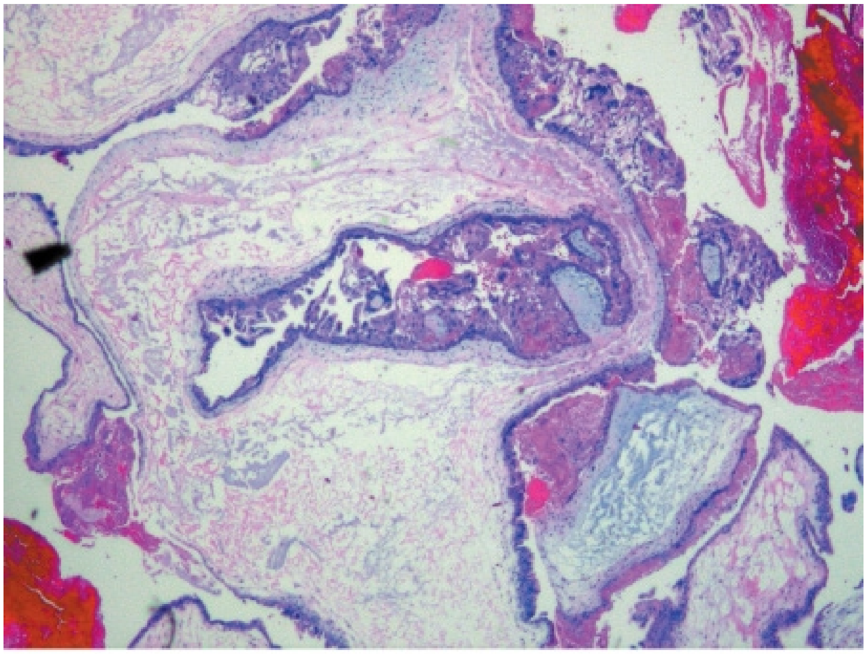


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Pathogenesis of complete and partial moles. **A** . A 46,XX complete mole may be formed if a 23,X-bearing sperm penetrates a 23,X-containing egg whose genes have become "inactive". Paternal chromosomes then duplicate to create a 46,XX chromosomal complement solely of paternal origin. Alternatively, this same type of egg can be fertilized independently by two sperm, either 23,X- or 23,Y-bearing, to create a 46,XX or 46,XY chromosomal complement, again of paternal origin only. **B** . A partial mole may be formed if two sperm, either 23,X- or 23,Y-bearing, both fertilize a 23,X-containing egg. The resulting fertilized egg is triploid. Alternatively, a similar haploid egg may be fertilized by an unreduced diploid 46,XY sperm. (Redrawn from le-Ming, 2002.).

Microscopically, complete moles display enlarged, edematous villi and abnormal trophoblastic proliferation that diffusely involve the entire placenta (Fig. 37-2). Macroscopically, these changes transform the chorionic villi into clusters of vesicles with variable dimensions. Indeed, the name *hydatidiform mole* stems from this "bunch of grapes" appearance. In these pregnancies, no fetal tissue or amnion is produced. As a result, this mass of placental tissue completely fills the endometrial cavity (Fig. 37-3).

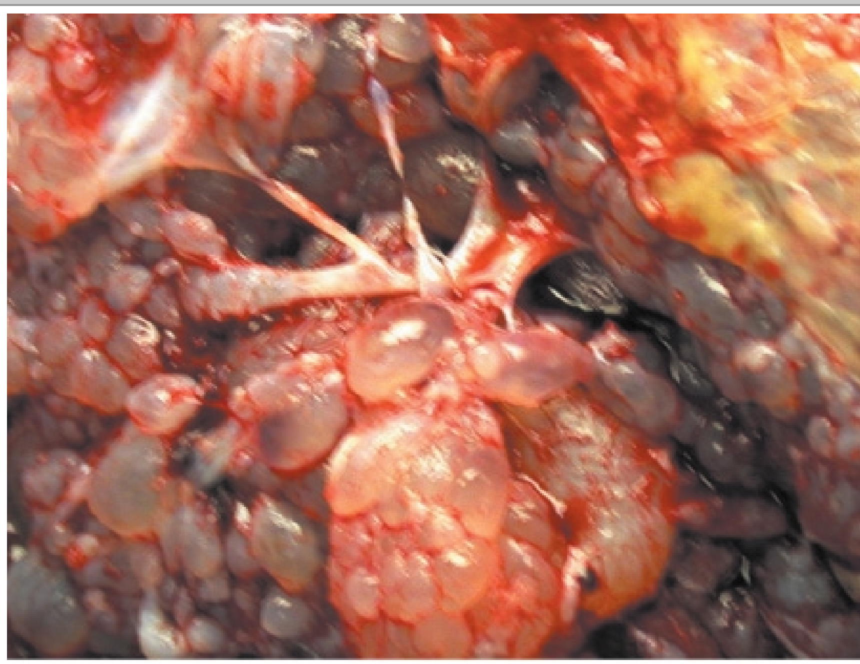
FIGURE 37-2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Histologic photograph of a complete hydatidiform mole. Villi have extensive stromal edema. *(Courtesy of Dr. Raheela Ashfaq.)*

FIGURE 37-3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photograph of gross complete hydatidiform mole specimen. Note the grape-like fluid filled clusters of chorionic villi. *(Courtesy of Dr. Raheela Ashfaq.)*

CLINICAL FINDINGS

The clinical presentation of a complete mole has changed considerably over the past few decades. More than half of patients diagnosed in the 1960s and 1970s had anemia and uterine sizes in excess of that predicted for their gestational age. In addition, hyperemesis gravidarum, preeclampsia, and theca-lutein cysts developed in approximately one quarter of women (Montz, 1988; Soto-Wright, 1995).

Complete moles, however, present infrequently today with these traditional signs and symptoms (Coukos, 1999). As a result of β-hCG testing and sonography, the mean gestational age at evacuation currently approximates 12 weeks, compared with 16 to 17 weeks in the 1960s and 1970s (Drake, 2006; Soto-Wright, 1995). Vaginal bleeding remains the most common symptom and still occurs in virtually all patients. One quarter of women will present with a uterine size greater than dates, but the incidence of anemia is less than 10 percent. Moreover, hyperemesis gravidarum, preeclampsia, and symptomatic theca-lutein cysts are observed rarely (Lazarus, 1999; Mosher, 1998; Soto-Wright, 1995). Currently, these sequelae typically occur chiefly in patients without early prenatal care who present with a more advanced gestational age and markedly elevated serum β-hCG levels (Osathanondh, 1986).

Plasma thyroxine levels are often elevated in women with complete moles, but clinical hyperthyroidism is unusual and is identified in only approximately 5 percent of patients (Amir, 1984; Berkowitz, 1987). In these circumstances, serum free thryoxine levels are elevated as a consequence of the thyrotropin-like effect of β-hCG (see Chap. 15, Peptide Hormones in Reproduction) (Hershman, 2004).

Partial Hydatidiform Mole

These moles vary from complete hydatidiform moles clinically, genetically, and histologically. The degree and extent of trophoblastic proliferation and villous edema are decreased compared with that in complete moles. Moreover, most partial moles contain fetal tissue and amnion in addition to placental tissues.

As a result, patients with partial moles typically present with signs and symptoms of an incomplete or missed abortion. Most women will have vaginal bleeding, but because trophoblastic proliferation is slight and only focal, uterine enlargement in excess of gestational age is uncommon. Similarly, preeclampsia, theca-lutein cysts, hyperthyroidism, and other dramatic clinical features are rare (Stefos, 2002). Pre-evacuation β-hCG levels are lower than those for complete moles and often do not exceed 100,000 mIU/mL. For this reason, partial moles are often not identified until after a histologic review of a curettage specimen.

Partial moles have a triploid karyotype (69,XXX, 69,XXY, or less commonly, 69,XYY) that is composed of one maternal and two paternal haploid sets of chromosomes (see Fig. 37-1) (Lawler, 1991). Nontriploid partial moles have been reported, but probably do not actually exist (Genest, 2002b). The coexisting fetus present with a partial mole is nonviable and typically has multiple malformations with abnormal growth (Jauniaux, 1999).

Differential Diagnosis

In reproductive-aged women with vaginal bleeding, diagnoses may include gynecologic causes of bleeding and complications of first-trimester pregnancy (see Chaps. 6, Threatened Abortion, and 8, Diagnosis). Therefore, initial urine or serum β-hCG measurement is invaluable in guiding the diagnostic evaluation.

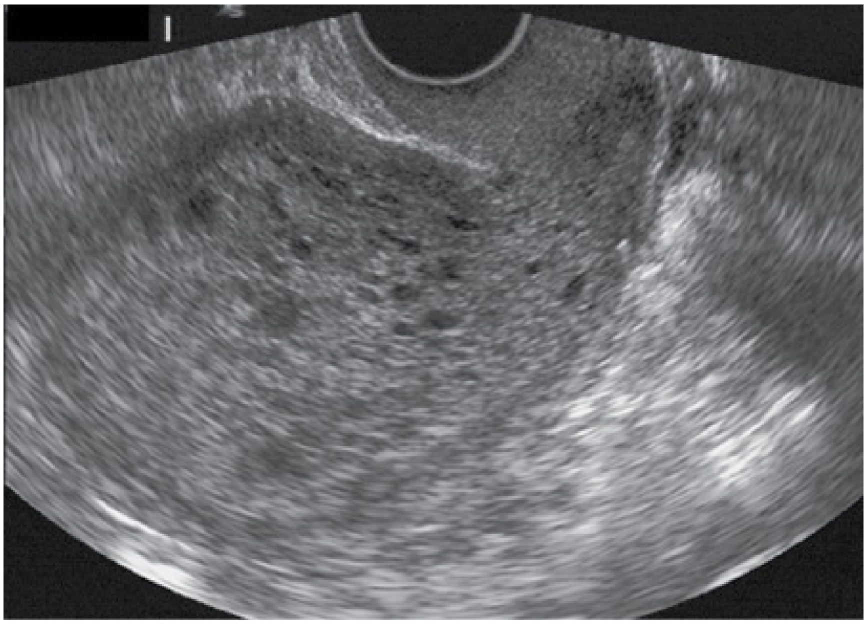
Diagnosis of Hydatidiform Mole

First-trimester diagnosis of hydatidiform mole is now common because of the routine use of serum β-hCG measurements and transvaginal sonography. An important characteristic of molar pregnancy is its tendency to produce excess β-hCG due to trophoblastic proliferation. As a result, serum β-hCG levels commonly are greater than that expected for the gestational age (Sasaki, 2003).

Although β-hCG levels are helpful, the diagnosis of molar pregnancy more frequently is found sonographically because of the

identifiable diffuse swelling and enlargement of the chorionic villi. Most first-trimester complete moles demonstrate a typical sonographic appearance: a complex, echogenic intrauterine mass containing many small cystic spaces. Fetal tissues and amnionic sac are absent (Fig. 37-4) (Benson, 2000). In contrast, sonographic features of a partial molar pregnancy include a thickened, hydropic placenta with a concomitant fetus (Zhou, 2005).

FIGURE 37-4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Sonogram of complete hydatidiform mole. The classic "snowstorm" appearance is created by the multiple placental vesicles, which completely fill this uterine cavity. *(Courtesy of Dr. Elysia Moschos.)*

Despite the utility of these tools, there are diagnostic limitations. For example, Lazarus and colleagues (1999) reported that β-hCG levels in early molar pregnancies may not always be elevated in the first trimester. These same investigators also found that sonography could lead to a false-negative diagnosis if performed at very early gestational ages, before the chorionic villi have attained the characteristic vesicular pattern (Lazarus, 1999). For example, only 20 to 30 percent of patients may have sonographic evidence suggestive of a partial mole (Johns, 2005; Lindholm, 1999; Sebire, 2001). Consequently, the preoperative diagnosis in early gestations is usually difficult and commonly not made until after a histologic review of the abortal specimen.

Pathologic Diagnosis

HISTOPATHOLOGY

The histopathologic changes typical of a complete and partial mole are listed in Table 37-2. There is no single criterion that distinguishes these hydatidiform moles from each other or from nonmolar gestations.

Complete moles characteristically have two prominent features: (1) trophoblastic proliferation and (2) hydropic villi. In gestations younger than 10 weeks, there are striking differences, however, from these classic findings. In these early gestations, hydropic villi may not be apparent, and molar stroma still may be vascular (Paradinas, 1997). As a result, complete moles now often must be characterized by more subtle morphologic alterations. Unfortunately, this can result in their misclassification as partial moles or nonmolar spontaneous abortions (Fukunaga, 2005; Mosher, 1998).

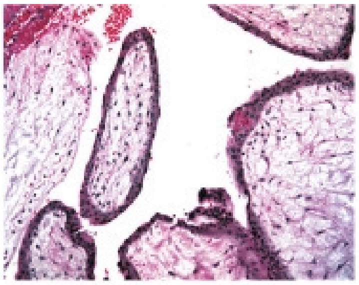
Partial moles are reliably diagnosed when three or four major diagnostic criteria are demonstrated: (1) two populations of villi, (2) enlarged, irregular, dysmorphic villi (with trophoblast inclusions), (3) enlarged, cavitated villi (≥3 to 4 mm), and (4)

syncytiotrophoblast hyperplasia/atypia (Chew, 2000). Good diagnostic reproducibility still can be achieved in most circumstances using these histologic distinctions of complete and partial mole.

PLOIDY DETERMINATION

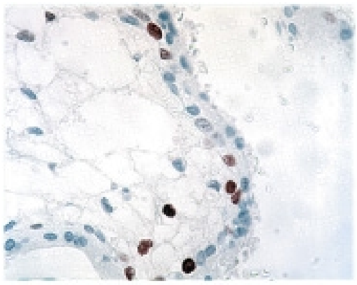
Determination of the type of molar gestation clearly can be enhanced by combining histopathology with ploidy determination. *Flow cytometry* is a technique for counting, examining, and sorting cells that are suspended in a stream of fluid. With this tool, multiple physical or chemical characteristics of single cells can be analyzed simultaneously as they flow through an optical electronic detection apparatus. A second cytometry method, *automated image cytometry,* uses optical images of several hundred cell nuclei to identify subtle morphologic changes within tissues. Both techniques can analyze cellular ploidy and can be used to distinguish complete moles (diploid) from partial moles (triploid) (Fig. 37-5). Automated image cytometry, however, has been shown to be more sensitive than flow cytometry in making this distinction (Crisp, 2003a).

FIGURE 37-5



A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



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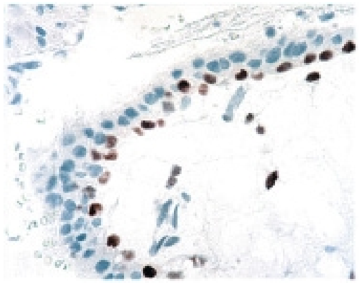

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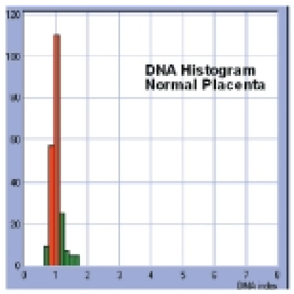

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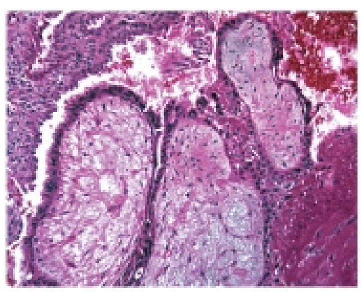

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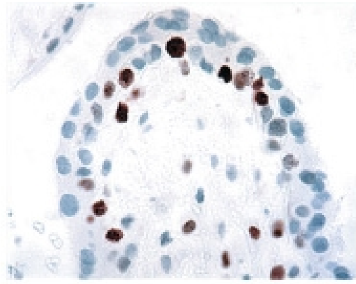

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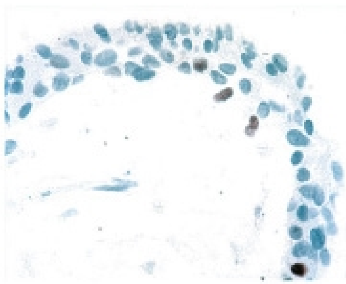

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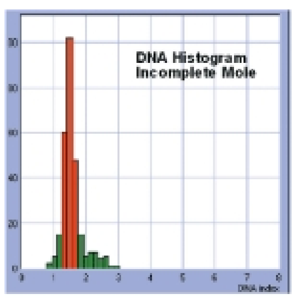

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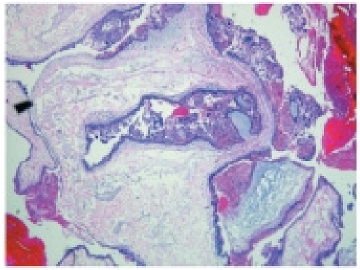

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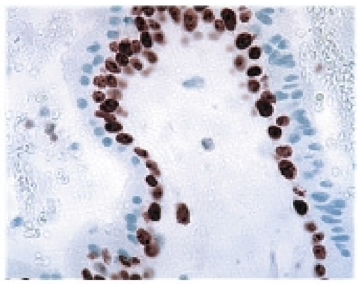

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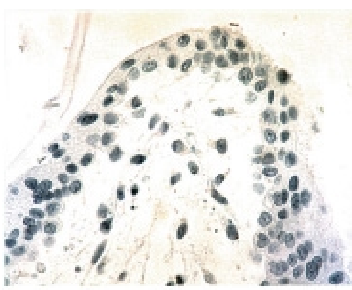

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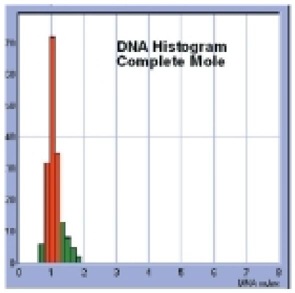


L

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Composite diagram of differences between normal hydropic products and partial or complete hydatidiform moles. Tissues that are negative for staining are blue, whereas those positive for staining are brown. The extent (percent cells staining) equates to low, medium, or high expression. Note the progressive increase in Ki-67 and a progressive reduction in p57KIP2 (p57) staining when comparing normal hydropic products of conception with partial and complete moles. First, KI-67 is a proliferation marker and is most prominently expressed in complete moles. In contrast, p57 is a nuclear protein whose gene is paternally imprinted and maternally expressed, meaning that the gene product is produced only in tissues containing a maternal allele. Because complete moles contain only paternal genes, the p57 protein is absent in complete moles. However, this nuclear protein is strongly expressed in spontaneous pregnancy losses with hydropic change. Finally, the DNA ploidy graphs show normal diploid pattern in hydropic contents and in complete moles, whereas the DNA peak is triploid (DNA index 1.5) in partial moles. *(Courtesy of Dr. Raheela Ashfaq.)*

IMMUNOSTAINING

In addition to ploidy analysis, histologic immunostaining techniques also can clarify the diagnosis. p57KIP2 is a nuclear protein whose gene is paternally imprinted and maternally expressed, meaning that the gene product is produced only in tissues containing a maternal allele. Because complete moles contain only paternal genes, the p57KIP2 protein is absent in complete moles (Merchant, 2005). In contrast, this nuclear protein is strongly expressed in normal placentas, spontaneous pregnancy losses with hydropic change, and partial hydatidiform moles (Castrillon, 2001). Accordingly, immunostaining for this nuclear protein is a practical and accurate adjunct to ploidy analysis in the pathologic classification of hydatidiform moles (Castrillon, 2001; Genest, 2002a). p57KIP2 staining has the additional advantage of differentiating hydropic abortuses from complete moles, a distinction not made by ploidy analysis (Merchant, 2005). As a result, complementary use of ploidy analysis and p57KIP2 status now can help to distinguish among a diploid hydropic spontaneous abortion (p57KIP2-positive), a diploid complete mole (p57KIP2-negative), and a triploid partial mole (p57KIP2-positive) (Fig. 37-5) (Crisp, 2003).

In summary, most complete and partial moles are readily identifiable and present little diagnostic difficulty. Those with borderline histology can be resampled in an attempt to confirm the classic features shown in Table 37-2. Ancillary testing with ploidy analysis or p57KIP2 staining is useful for diagnostic, educational, and quality assurance purposes, but these adjunctive tests should not become the mandatory "gold standard" for routine clinical practice because they are neither perfect nor universally available (Genest, 2001).

Treatment

Suction curettage is the preferred method of evacuation regardless of uterine size in patients who wish to remain fertile (Tidy, 2000). Other surgical procedures, however, may be employed for specific indications. For example, hysterectomy may be performed with preservation of the ovaries if a woman wishes surgical sterilization. Additionally, theca-lutein ovarian cysts regress after delivery but may be aspirated if symptomatic (Berkowitz, 1996). Oophorectomy, however, should not be performed except for rare circumstances when torsion of an ovary enlarged by theca-lutein cysts leads to extensive ovarian infarction (Mungan, 1996).

Prior to surgery, patients are evaluated for the presence of associated medical complications. Fortunately, thyroid storm from untreated hyperthyroidism, respiratory insufficiency from trophoblastic emboli, and other severe coexisting conditions are rare. Because of the tremendous vascularity of these placentas, blood products should be available prior to the evacuation of larger

moles, and adequate infusion lines should be established.

At the beginning of the evacuation, the cervix is dilated to admit a 10- to 12-mm plastic Karmen suction cannula (see Fig. 41-17.3). As aspiration of molar tissues ensues, intravenous oxytocin is given. At our institution, 20 units of synthetic oxytocin is mixed with 1 L of crystalloid and infused at rates to achieve uterine contraction. Finally, a thorough, gentle curettage is performed (see Section 41-17, Suction Dilatation and Curettage). Intraoperative sonography may assist in documenting complete evacuation.

Following curettage, because of the possibility of partial mole and its attendant fetal tissue, Rh immune globulin should be given to nonsensitized RhD-negative women. Rh immune globulin, however, may be withheld if the diagnosis of complete mole is certain (Fung Kee, 2003).

Postmolar Surveillance

INCIDENCE OF GESTATIONAL TROPHOBLASTIC NEOPLASIA FOLLOWING HYDATIDIFORM MOLE

Gestational trophoblastic neoplasia (GTN) develops after approximately 15 to 20 percent of complete moles (Soto-Wright, 1995; Wolfberg, 2004). Despite the trend of diagnosing these abnormal pregnancies at earlier gestational ages, this incidence has not decreased (Seckl, 2004; Soto-Wright, 1995). Of those women who develop GTN, three quarters have locally invasive molar disease, and the remaining one quarter develop metastases.

In contrast, GTN develops in only 2 to 4 percent of partial moles following evacuation (Goto, 1993; Lavie, 2005). A lower reported incidence (0.5 percent) of GTN following partial mole in the United Kingdom may reflect more stringent diagnostic criteria (Bagshawe, 1990; Seckl, 2000). Malignant transformation into metastastic choriocarcinoma does occur but fortunately is exceedingly rare (0.1 percent) (Cheung, 2004; Seckl, 2000).

BETA-HUMAN CHORIONIC GONADOTROPIN LEVELS

There are no pathologic or clinical features at presentation that accurately predict which patients ultimately will develop GTN (Rice, 1990). Because of the trophoblastic proliferation that characterizes these neoplasms, serial serum β-hCG levels following evacuation can be used to effectively monitor patients for development of GTN. Therefore, postmolar surveillance with serial quantitative serum β-hCG levels should be the standard. Titers should be monitored following uterine evacuation at least every 1 to 2 weeks until they become undetectable.

Historically, 6 months of surveillance after achieving an undetectable β-hCG levels was recommended for all patients with molar gestation. Unfortunately, poor compliance with 6 months of monitoring has been reportedâ€"especially among indigent women and certain ethnic groups (Allen, 2003; Massad, 2000). In addition, pregnancies conceived within 6 months of achieving undetectable β-hCG levels complicate the monitoring schedule but are otherwise uneventful (Tuncer, 1999). As a result, several studies have evaluated and recent data support the safety of significantly shortening the duration of surveillance. It appears that a single blood sample demonstrating an undetectable level of β-hCG following molar evacuation is sufficient to exclude the possibility of progression to GTN. Patients may then be discharged safely from routine surveillance thereafter (Batorfi, 2004; Feltmate, 2003; Lavie, 2005; Wolfberg, 2004).

Pregnancies can occur during the monitoring period, and the resulting β-hCG production can hinder detection of progression to GTN (Allen, 2003). For this reason, women are encouraged to use effective contraception until achieving a β-hCG titer of less than 5 mIU/mL or the threshold of the individual assay. Oral contraceptive pills decrease the likelihood of pregnancy compared with less effective barrier contraception and do not increase the risk of GTN (Curry, 1989). Injectable medroxyprogesterone acetate is particularly useful when poor compliance is anticipated (Massad, 2000). In contrast, intrauterine devices are not to be inserted until the β-hCG level is undetectable because of the risk of uterine perforation if an invasive mole is present.

Prophylactic Chemotherapy

The purpose of administering chemotherapy at the time of molar evacuation is to prevent the development of GTN in high-risk patients who are unlikely to be compliant with β-hCG surveillance. For example, in a prospective, double-blind clinical trial of 60 women who had high-risk complete moles, Limpongsanurak (2001) randomly assigned women to receive either dactinomycin or

placebo at the time of evacuation. Prophylactic chemotherapy reduced the incidence of GTN from 50 to 14 percent, but toxicity was significant. In clinical practice, the correct classification of high-risk complete moles, however, is extremely difficult because there is no universally accepted combination of risk factors that accurately predicts GTN development. Moreover, regardless of how a high-risk complete mole is defined, few women ultimately will be assigned to this group. Thus, identification at diagnosis of the women who potentially could benefit from prophylactic chemotherapy is of little overall clinical importance (Parazzini, 1988b).

As a result, the indications for prophylactic chemotherapy remain controversial (Murad, 1990). Rarely, this strategy may be considered in patients with complete moles and multiple risk factors (age greater than 40 years, previous history of molar pregnancy, and excessively high β-hCG titer), particularly if postevacuation β-hCG testing is unavailable or poor compliance during surveillance is expected (Berkowitz, 1996). For this reason, prophylactic chemotherapy is not offered routinely and typically is practiced outside the United States and Europe (Uberti, 2006).

Ectopic Molar Pregnancy

The true incidence of ectopic gestational trophoblastic disease approximates 1.5 per 1 million births (Gillespie, 2004). More than 90 percent of suspected cases will reflect an overdiagnosis of florid extravillous trophoblastic proliferation in the fallopian tube (Burton, 2001; Sebire, 2005b). Other sites of ectopic implantation are even less common (Bailey, 2003). As with any ectopic pregnancy, initial management usually involves surgical removal of the conceptus and histopathologic evaluation.

Coexisting Fetus

The estimated incidence of twin pregnancy consisting of hydatidiform mole and a coexisting fetus is 1 per 20,000 to 100,000 pregnancies. Sebire (2002b) described the outcome of 77 twin pregnancies, each composed of a complete mole and a healthy co-twin. Of this group, 24 women chose to have an elective termination, and 53 continued their pregnancies. Twenty-three gestations aborted spontaneously at less than 24 weeks, 2 were terminated because of severe preeclampsia, and 28 pregnancies lasted at least 24 weeksâ€”resulting in 20 live births. The authors demonstrated that coexisting complete moles and healthy co-twin pregnancies have a high risk of spontaneous abortion, but approximately 40 percent result in live births.

In this study, the risk of progression to GTN was 16 percent in first-trimester terminations and not significantly higher (21 percent) in women who continued their pregnancies. Previous reports with fewer patients had suggested a higher risk of developing GTN in those continuing their pregnancies (Matsui, 2000; Steller, 1994). Because the risk of malignancy is unchanged with advancement of gestational age, pregnancy continuation may be allowed, provided that severe maternal complications are controlled and fetal growth is normal. Fetal karyotyping to confirm a normal chromosomal pattern is also recommended (Marcorelles, 2005; Matsui, 2000).

GESTATIONAL TROPHOBLASTIC NEOPLASIA

This term encompasses primarily pathologic entities that are characterized by aggressive invasion of the endometrium and myometrium by trophoblastic cells. Histologic categories include common tumors such as the *invasive mole* and *gestational choriocarcinoma,* as well as the rare *placental site trophoblastic tumor* and *epithelioid trophoblastic tumor.* Although these histologic types have been characterized and described, in most cases of GTN there is no tissue available for pathologic study. For this reason, most cases of GTN are diagnosed and managed clinically.

Gestational trophoblastic neoplasia typically develops with or follows some form of pregnancy, but occasionally, an antecedent gestation cannot be confirmed with certainty. Most of cases follow a hydatidiform mole. Rarely, GTN develops after a live birth, miscarriage, or termination. Many of the reported nonmolar cases actually may represent disease due to an unrecognized early molar pregnancy (Sebire, 2005a).

Histologic Classification

INVASIVE MOLE

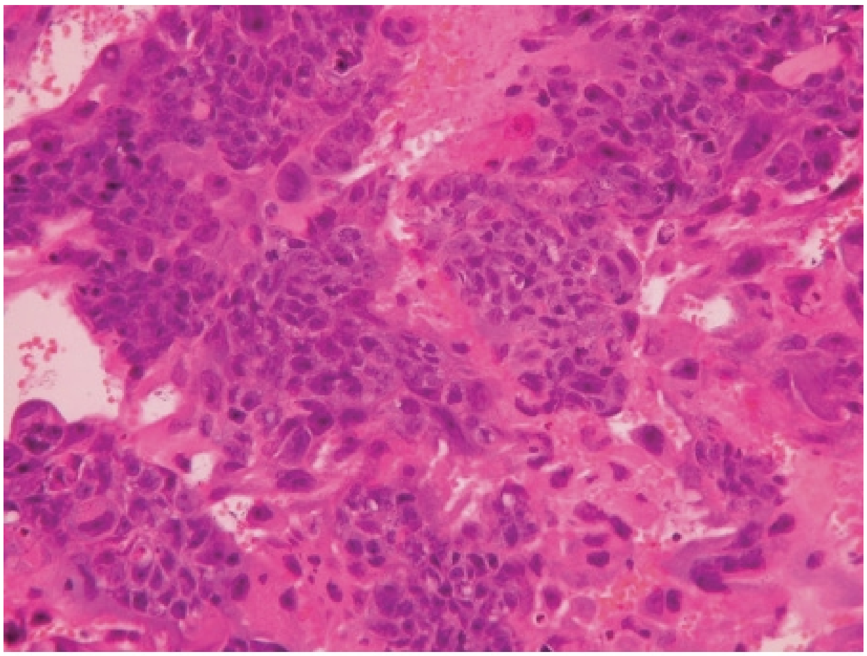
This is a common manifestation of GTN characterized by the presence of whole chorionic villi that accompany excessive trophoblastic overgrowth and invasion. These tissues penetrate deep into the myometrium, sometimes involving the peritoneum, adjacent parametrium, or vaginal vault. Such moles are locally invasive but generally lack the pronounced tendency to develop

widespread metastases typical of choriocarcinoma. Invasive moles originate almost exclusively from complete or partial molar gestations (Sebire, 2005a).

GESTATIONAL CHORIOCARCINOMA

This extremely malignant tumor is comprised of sheets of anaplastic cytotrophoblast and syncytiotrophoblast cells with prominent hemorrhage, necrosis, and vascular invasion (Fig. 37-6). Unlike molar disease, however, chorionic villi are characteristically absent. Gestational choriocarcinomas initially invade the endometrium and myometrium but tend to develop early blood-borne systemic metastases (Fig. 37-7).

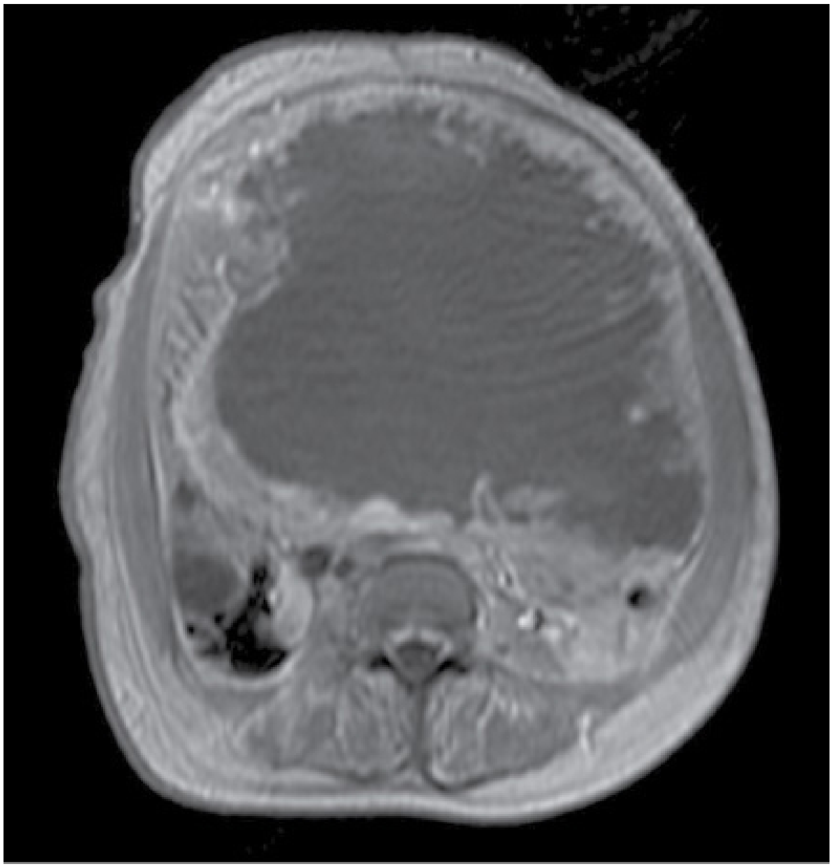
FIGURE 37-6



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photomicrograph of choriocarcinoma. Characteristic histologic features of include abnormal cytotrophoblastic proliferation capped by syncytiotrophoblasts. These tumors are very vascular; note abundant blood in the background. *(Courtesy of Dr. Raheela Ashfaq.)*

FIGURE 37-7



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Computed-tomography (CT) scan of choriocarcinoma invading the uterus.

Although most cases develop following evacuation of a molar pregnancy, these tumors also may less commonly follow a nonmolar pregnancy. Alternatively, primary "nongestational" choriocarcinoma ovarian germ cell tumors have an identical histologic appearance and are in part distinguished by the absence of any preceding pregnancy event (see Chap 36, Choriocarcinoma).

Gestational choriocarcinoma develops in approximately 1 in 30,000 nonmolar pregnancies. Two thirds of such cases follow term pregnancies, and a third develop after a spontaneous abortion or pregnancy termination. Tidy (1995) reviewed 100 patients with nonmolar gestational choriocarcinoma and found that 62 presented after a live birth, 6 after a live birth preceded by a molar pregnancy, and 32 after a nonmolar abortion. Vaginal bleeding was the most common symptom in all groups (Tidy, 1995). For this reason, abnormal bleeding for more than 6 weeks following any pregnancy should be evaluated with β-hCG testing to exclude a new pregnancy or GTN (Soper, 2004).

In those cases following term pregnancies, unanticipated choriocarcinoma is detected occasionally in an otherwise normal-appearing placenta at delivery. More commonly, however, the diagnosis of choriocarcinoma is delayed due to subtle signs and symptoms of disease in patients with an antecedent normal pregnancy. For example, Rodabaugh and colleagues (1998) found that in 89 percent of cases, the preceding pregnancy had produced an uncomplicated live birth. Hydrops, however, was a notable complication in the remaining fetuses.

In part because of the typical delay to diagnosis, choriocarcinomas following term pregnancies have a significantly higher mortality rate than GTN following nonmolar abortions (Olive, 1984; Tidy, 1995). Rodabaugh and associates (1998) at the New England

Trophoblastic Disease Center reported a 14-percent mortality rate in 44 women diagnosed with choriocarcinoma following a term pregnancy. More than half of the patients presenting with brain metastases or placental site trophoblastic tumors have a preceding term gestation (Feltmate, 2001; Newlands, 2002). The frequency of these high-risk features also helps to explain the poorer prognosis for choriocarcinoma following a term pregnancy.

PLACENTAL SITE TROPHOBLASTIC TUMOR

This tumor consists predominantly of intermediate trophoblasts at the placental site and is a rare variant of GTN with unique disease behavior (Scully, 1981). Placental site trophoblastic tumors can follow any type of pregnancy but develop more commonly following a normal pregnancy. They tend to infiltrate only within the uterus, disseminate late in their course, and produce low levels of β-hCG relative to their mass (Twiggs, 1998). When this tumor does spread, however, the pattern mirrors that of gestational choriocarcinoma. Fifteen percent of all reported cases were fatal (Baergen, 2006).

Hysterectomy is the primary method of treatment for nonmetastatic placental site trophoblastic tumor due to its relative insensitivity to chemotherapy (Feltmate, 2001; Papadopoulos, 2002). Alternatively, the combination of operative hysteroscopic resection followed by chemotherapy may be an option to preserve fertility in particularly motivated patients (Machtinger, 2005).

Metastatic placental site trophoblastic tumor has a much poorer prognosis than the other, more common, types of metastatic GTN (Hassadia, 2005). As a result, aggressive combination chemotherapy is indicated. A regimen of etoposide, methotrexate, and dactinomycin alternating with etoposide and cisplatin (EMA/EP) is the most effective treatment (Newlands, 2000). Radiation, however, also may have a role in some situations. Papadopoulos and colleagues (2002) have reported a 79-percent survival rate in 34 patients treated by multimodality therapy.

EPITHELIOID TROPHOBLASTIC TUMOR

This rare trophoblastic tumor is distinct from gestational choriocarcinoma and placental site trophoblastic tumor. The preceding pregnancy event may be remote, or in some cases a prior gestation cannot be confirmed. Epithelioid trophoblastic tumor develops from neoplastic transformation of chorionic-type intermediate trophoblast. Microscopically, this tumor resembles placental site trophoblastic tumor, but the cells are smaller and display less nuclear pleomorphism. Grossly, epithelioid trophoblastic tumor grows in a nodular fashion rather than the infiltrative pattern of placental site trophoblastic tumor. Hysterectomy is the primary method of treatment, but approximately 20 to 25 percent of patients will present with metastatic disease. Currently, there are too few reported cases to evaluate the efficacy of chemotherapy (Shih, 1998).

Clinical Classification

DIAGNOSIS

Most GTN cases are diagnosed clinically using hormonal evidence of persistent trophoblastic tissue (Table 37-3). Tissue is infrequently available for pathologic diagnosis. As a result, most centers in the United States diagnose GTN on the basis of rising β-hCG values or a persistent plateau of β-hCG values for at least 3 weeks. Unfortunately, there is a lack of uniformity in the definition of a persistent plateau. Additionally, the diagnostic criteria are less stringent in the United States than in Europe partly because of concern that some patients may be lost to follow-up if stricter criteria are used.

Table 37-3 Criteria for the Diagnosis of Gestational Trophoblastic Neoplasia
1. Plateau of β-hCG lasts for four measurements over a period of 3 weeks or longer (days 1, 7, 14, and 21).
2. Rise of β-hCG of 3 weekly consecutive measurements or longer, over a period of 2 weeks or more (days 1, 7, and 14).
3. β-hCG remains elevated for 6 months or more.
4. Histologic diagnosis of choriocarcinoma.

FIGO=International Federation of Gynecology and Obstetrics; hCG= beta human chorionic gonadotropin. From FIGO Oncology Committee, 2002, with permission.

When serologic criteria are met for GTN, a new intrauterine pregnancy should be excluded using β-hCG levels correlated with

sonographic findings, especially when there has been a long delay in monitoring of serial β-hCG levels or noncompliance with contraception or both.

DIAGNOSTIC EVALUATION

Patients with GTN undergo a thorough pretreatment assessment to determine the extent of disease. The initial evaluation includes a pelvic examination, chest radiograph, and abdominal-pelvic computed tomographic (CT) scan (Garner, 2004; Ngan, 1998). Pulmonary lesions should prompt CT scanning of the chest and brain. In addition, positron-emission tomography/computed tomography (PET/CT) may be useful in the evaluation of occult choriocarcinoma when conventional imaging fails to identify metastatic disease (Numnum, 2005).

STAGING

Gestational trophoblastic neoplasia is staged anatomically based on a system adopted by the International Federation of Gynecology and Obstetrics (FIGO) (Table 37-4). Patients at low risk for therapeutic failure are distinguished from those at high risk using the modified prognostic scoring system of the World Health Organization (WHO) (Table 37-5). Patients with WHO scores of 0 to 6 are considered to have low-risk disease, whereas those with a score of 7 or higher are assigned to the high-risk GTN group. For the most accurate description of these patients, the Roman numeral corresponding to FIGO stage is separated by a colon from the sum of all the actual risk factor scoresâ€œfor example, stage II:4 or stage IV:9 (FIGO Oncology Committee, 2002).

Table 37-4 FIGO Anatomic Staging

Stage I	Disease confined to the uterus
Stage II	GTN extends outside of the uterus but is limited to the genital structures (adnexa, vagina, broad ligament)
Stage III	GTN extends to the lungs, with or without known genital tract involvement
Stage IV	All other metastatic sites (brain, liver)

FIGO = International Federation of Gynecology and Obstetrics; GTN = gestational trophoblastic neoplasia.

Table 37-5 Modified WHO Prognostic Scoring System as Adapted by FIGO

Scores	**0**	**1**	**2**	**4**
Age (yr)	<40	≥40	â€”	â€”
Antecedent pregnancy	Mole	Abortion	Term	â€”
Interval months from index pregnancy	<4	4â€œ6	7â€œ12	≥13
Pretreatment serum β-hCG (mIU/mL)	$<10^3$	10^3 â€œ$<10^4$	10^4 â€œ$<10^5$	$\geq 10^5$
Largest tumor size (including uterus)	â€”	3â€œ<5 cm	≥5 cm	â€”
Site of metastases	Lung	Spleen, kidney	Gastro-intestinal	Liver, brain
Number of metastases	â€”	1â€œ4	5â€œ8	>8
Previous failed chemotherapy drugs	â€”	â€”	1	≥2

Low risk = WHO score of 0 to 6; high risk = WHO score of ≥ 7.

FIGO = International Federation of Gynecology and Obstetrics; hCG = human chorionic gonadotropin; WHO = World Health Organization.

This addition of risk scoring to anatomic staging has been shown to best reflect the disease behavior (Ngan, 2004). Women with high risk scores are more likely to have tumors that are resistant to single-agent chemotherapy. They are therefore treated initially with combination chemotherapy. Although patients with stage I disease infrequently have a high risk score, those with stage IV disease invariably have a high risk score.

The FIGO classification system has been reported to be a better predictor of disease-free survival than the WHO scoring system (Bjorge, 2002). Women diagnosed with FIGO stage I, II, and III GTN have a survival rate approaching 100 percent (Table 37-6) (Berkowitz, 1996).

Table 37-6 Survival of Gestational Trophoblastic Neoplasia by FIGO Stage

Stage	Survival	Percent
I	424/424	100
II	27/27	100
III	130/131	99
IV	14/18	78

FIGO = International Federation of Gynecology and Obstetrics.

From Berkowitz, 1996, with permission.

NONMETASTATIC DISEASE

Invasive moles arising from complete molar gestations comprise most cases of nonmetastatic GTN. Fifteen to 20 percent of complete moles develop locally invasive disease after evacuation, compared with only 2 to 4 percent of partial moles. Placental site trophoblastic tumors and epithelioid trophoblastic tumors are other rarer causes of nonmetastatic GTN. Locally invasive trophoblastic tumors may perforate through the myometrium and lead to intraperitoneal bleeding (Mackenzie, 1993). Alternatively, vaginal hemorrhage can follow tumor erosion into uterine vessels, or necrotic tumor may involve the uterine wall and serve as a nidus for infection. Fortunately, the prognosis is excellent for all types of nonmetastatic disease despite these possible manifestations (Lurain, 1982).

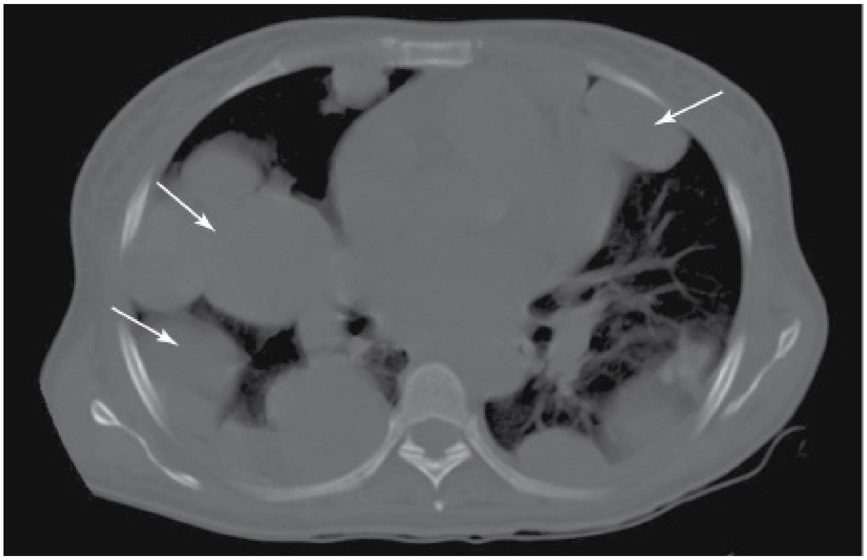
METASTATIC DISEASE

Choriocarcinomas originating from complete molar gestations comprise most cases of metastatic GTN. Four to five percent of complete moles develop metastatic choriocarcinoma after evacuation. The incidence following any other type of molar or nonmolar gestation is exceedingly rare. Choriocarcinomas have a propensity to distant spread and should be suspected in any woman of reproductive age with metastatic disease from an unknown primary (Tidy, 1995). Moreover, because of this tendency, chemotherapy is indicated whenever choriocarcinoma is diagnosed histologically.

Although many patients are largely asymptomatic, metastatic GTN is highly vascular and prone to severe hemorrhage either spontaneously or during biopsy. Menorrhagia is a common presenting symptom. The most common sites of spread are the lungs (80 percent), vagina (30 percent), pelvis (20 percent), liver (10 percent), and brain (10 percent) (Fig. 37-8). Patients with pulmonary metastases typically have asymptomatic lesions identified on routine chest radiograph and infrequently present with cough, dyspnea, hemoptysis, or signs of pulmonary hypertension (Kumar, 1988). In patients with the early development of respiratory failure that requires intubation, the overall outcome is poor. Hepatic or cerebral involvement is encountered almost exclusively in patients who have had an antecedent nonmolar pregnancy and a protracted delay in tumor diagnosis (Newlands,

2002). These women may present with associated hemorrhagic events. Virtually all patients with hepatic or cerebral metastases have concurrent pulmonary or vaginal involvement or both. Great caution is used in attempting excision of any metastatic disease site due to the risk of profuse hemorrhage. Thus, this practice is almost uniformly avoided except in extenuating circumstances of life-threatening brain stem herniation or chemotherapy-resistant disease.

FIGURE 37-8



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Computed-tomography (CT) scan of metastatic disease to the lung. Arrows point to some of the multiple lesions.

Treatment

SURGICAL MANAGEMENT

Most patients diagnosed with postmolar GTN have persistent tumor confined to the endometrial cavity and are treated primarily with chemotherapeutic agents. Repeat dilatation and curettage generally are avoided to prevent morbidity and mortality caused by uterine perforation, hemorrhage, infection, uterine adhesions, and anesthetic complications (Soper, 2004). Accordingly, second evacuations typically are not performed in the United States unless patients have persistent uterine bleeding and substantial amounts of retained molar tissue. Repeat uterine curettage is a much more standard part of the management of postmolar GTN in Europe and has been shown to reduce significantly both the number of patients needing any further treatment and the number of courses in those who do require chemotherapy (Pezeshki, 2004; van Trommel, 2005). A second evacuation followed by continued surveillance, however, is a less attractive option for poorly compliant patients than single-agent chemotherapy (Allen, 2003; Massad, 2000).

Hysterectomy may play several roles in the treatment of GTN. First, it may be performed primarily to treat placental site trophoblastic tumors, epithelioid trophoblastic tumors, or chemotherapy-resistant disease. In addition, severe uncontrollable vaginal or intra-abdominal bleeding may necessitate hysterectomy as an emergency procedure (Chao, 2002). Because of these more extreme indications, most women undergoing hysterectomy have elevated pretreatment risk scores, unusual pathology, and higher mortality (Pisal, 2002). Finally, adjuvant hysterectomy decreases the total dose of chemotherapy needed to achieve clinical remission in low-risk GTN. Patients with disease apparently confined to the uterus who do not desire future fertility should be counseled about this option (Suzuka, 2001).

Residual lung metastases may persist in 10 to 20 percent of patients achieving clinical remission of GTN after completion of chemotherapy. An undetectable β-hCG reflects clinical remission. These patients do not appear to have an increased risk of relapse

compared with those having normal chest radiographs or CT scans. Thoracotomy is not required in these situations (Powles, 2006). Surgical resection of metastases is performed only when chemotherapy-resistant disease is suspected.

CHEMOTHERAPY FOR LOW-RISK GTN

Methotrexate

This agent is the most common treatment for low-risk disease. Several intramuscular regimens have been reported, with complete remission rates ranging from 60 to 80 percent (Table 37-7). The Gynecologic Oncology Group (GOG) conducted a prospective cohort study (protocol 79) of weekly methotrexate that established an effective dose of 30 mg/m^2 with minimal toxicity (Homesley, 1988, 1990). Charing Cross Hospital investigators use an 8-day alternating regimen of methotrexate 50 mg on treatment days 1, 3, 5, and 7 and oral folinic acid 7.5 mg taken orally on days 2, 4, 6, and 8. Treatment is repeated every 2 weeks until β-hCG is undetectable (McNeish, 2002). University of Sheffield investigators demonstrated similar success with the same regimen (Khan, 2003). Alternatively, intramuscular methotrexate 0.4 mg/kg per day for 5 consecutive days on alternating weeks is another effective option, but it requires a median of 20 to 30 clinic visits for chemotherapy administration to achieve remission (Schorge, 2003; Soper, 1994a).

Table 37-7 Intramuscular Methotrexate Regimens for Treatment of Low-Risk GTN

Frequency	Dose	Population Studied	CR Rate (%)	First Author
Weekly	30â€“50 mg/m^2	Nonmetastatic GTN	74â€“81	Homesley, 1988
Days 1,3,5,7	50 mg/d	Low-risk GTN	67â€“72	McNeish, 2002
				Khan, 2003
5-Day	0.4 mg/kg/d	Low-risk GTN (majority)	60	Soper, 1994a

CR = clinical remission (calculated for first-line treatment without needing alternative chemotherapy); GTN = gestational trophoblastic neoplasia.

As discussed more fully in Chapter 27, Methotrexate, methotrexate is a folic acid antagonist that inhibits DNA synthesis by causing an acute intracellular deficiency of folate coenzymes. Mild stomatitis is the most common side effect, but other serosal symptoms, especially pleurisy, develop in up to one quarter of patients treated with low-dose methotrexate. Pericarditis, peritonitis, and pneumonitis are infrequent (Sharma, 1999). Toxicity develops more frequently with the more intense daily regimens compared with weekly administration despite routine folinic acid "rescue" of normal mucosal and serosal cells (Gleeson, 1993).

In addition to intramuscular administration, methotrexate intravenous infusion has proved successful. For example, a 100 mg/m^2 bolus followed by 200 mg/m^2 given during 12 hours has a 65-percent complete response rate (Garrett, 2002). Folinic acid rescue is not necessary using this regimen due to the nontoxic levels of methotrexate reached 24 hours after infusion (Allen, 2003; Wong, 2000). Because this regimen is usually successful with a single dose, it may be particularly effective in poorly compliant patients by shortening the treatment duration and reducing the number of required visits (Schorge, 2003). Oral methotrexate has few indications in the management of GTN (Farley, 2005).

Dactinomycin

This chemotherapy agent is used less commonly for the primary treatment of low-risk disease. The GOG conducted a phase II trial of "pulse" dactinomycin, 1.25 mg/m^2 administered as an intravenous bolus dose every 2 weeks (protocol 69). Ninety-four percent of patients without metastatic disease achieved remission (Petrilli, 1987). In addition, dactinomycin was superior to methotrexate in a recent prospective study of 46 patients. Investigators found that the pulse dactinomycin arm had a 94-percent success rate compared with a 50-percent success rate for weekly intramuscular methotrexate given in doses of 30 mg/m^2 (Gilani, 2005). The GOG is currently performing a larger prospective, randomized study (protocol 174) using the same dactinomycin and methotrexate regimens for low-risk GTN to directly compare treatment efficacy and toxicity. Pulse dactinomycin has similar efficacy as a 5-day course of dactinomycin, 12 μg/kg each day, but is considered the treatment of choice because of its greater convenience and lower

cost (Schlaerth, 1984).

Patients who do not respond to an initial single-agent chemotherapeutic regimen should have their score recalculated using the modified WHO prognostic scoring system. Most women still will be considered low risk and may be switched to single-agent second-line therapy. Methotrexate-resistant GTN often responds to dactinomycin (Chen, 2004). The GOG recently demonstrated a 73-percent success rate in a phase II trial of pulse dactinomycin as salvage treatment for 40 patients with methotrexate-resistant GTN (protocol 176). Etoposide is used less commonly in this setting but is also effective (Mangili, 1996). Patients treated initially with pulse dactinomycin who develop resistant GTN still may be treated successfully with the 5-day course of dactinomycin (Kohorn, 2002). Alternatively, single-agent methotrexate or etoposide is effective in these cases (Matsui, 2005).

CHEMOTHERAPY FOR HIGH-RISK GTN

Etoposide, methotrexate, and dactinomycin alternating with cyclophosphamide and vincristine (EMA/CO) chemotherapy is a well-tolerated and highly effective regimen for high-risk GTN that should be considered the primary treatment in most circumstances (see Chap 27, Cyclophosphamide). Response rates are comparable whether patients are treated primarily or after failure of single-agent chemotherapy. Bower and colleagues (1997) reported a 78-percent complete remission rate in 272 consecutive women. Similarly, other investigators have observed a 71- to 77-percent complete remission rate (Escobar, 2003; Soper, 1994b).

Patients with high-risk disease who become refractory to or relapse from EMA/CO chemotherapy may be treated effectively by replacing the cyclophosphamide and vincristine component with etoposide and cisplatin (EMA/EP). Newlands and colleagues (2000) reported an 88-percent survival rate among 34 patients using this regimen. Other alternatives for second- or third-line therapy include paclitaxel and alternating etoposide and cisplatin (TE/TP) and cisplatin and bleomycin combined with either vinblastine (VPB) or etoposide (BEP) (Azab, 1989; DuBeshter, 1989; Lurain, 2005; Osborne, 2004). High-dose chemotherapy and hematopoietic stem cell support are unproven for refractory GTN (El Helw, 2005).

BRAIN METASTASES

Patients with GTN metastatic to the brain usually can be cured with aggressive multimodality therapy that may include chemotherapy, surgery, and radiation. In addition, emergency craniotomy may be indicated in selected patients who display rapidly deteriorating signs (Semple, 2004; Yang, 2005).

Newlands and colleagues (2002) reported an 80-percent survival rate among 39 patients treated by EMA/CO with an escalated dose of methotrexate and folinic acid. Intrathecal methotrexate also was administered until β-hCG levels were undetectable. Surgical removal of the main active site of disease was performed in 16 patients. Four of the 39 women died within 8 days of presentation. The presence of both liver and brain metastases was a particularly adverse prognostic combination, with only 1 of 5 patients surviving. Whole-brain radiation therapy also may be an efficacious adjunct to combination chemotherapy and surgery, but at the cost of inducing intellectual impairment in patients who are cured (Evans, 1995; Schechter, 1998).

POSTTREATMENT SURVEILLANCE

Monitoring of patients with stage I, II, or III GTN consists of weekly β-hCG measurements until the level is undetectable for 3 weeks, followed by monthly titers until the level is undetectable for 12 months. Women with stage IV disease are followed for 24 months because of the greater risk of late relapse. Patients are encouraged to use effective contraception, as outlined earlier, during the entire surveillance period (Berkowitz, 1996).

SUBSEQUENT PREGNANCY OUTCOME

Patients may expect a normal reproductive outcome after achieving remission from gestational trophoblastic disease. Women having a pregnancy affected by a histologically confirmed complete or partial mole may be counseled that the risk of a repeat mole in a subsequent pregnancy is 1 to 2 percent (Berkowitz, 1994). Most will be of the same type of mole as the preceding pregnancy (Sebire, 2003). Pregnancy after combination EMA/CO chemotherapy for GTN also has a high probability of success and a favorable outcome (Lok, 2003).

SECONDARY TUMORS

Etoposide-based combination chemotherapy has been associated with an increased risk of leukemia, colon cancer, melanoma, and

breast cancer up to 25 years after treatment for GTN. An overall 50-percent excess risk was observed (Rustin, 1996). Etoposide therefore is reserved to treat patients who are likely to be resistant to single-agent chemotherapy and, in particular, patients with high-risk metastatic disease (Schorge, 2000).

PHANTOM β-HCG

Occasionally, persistent mild elevations of serum β-hCG are detected that lead physicians erroneously to treat patients with cytotoxic chemotherapy or hysterectomy or both when, in reality, no true β-hCG or trophoblastic disease is present (Cole, 1998; Rotmensch, 2000). This "phantom" β-hCG reading results from the presence in serum of heterophilic antibodies that interfere with the β-hCG immunoassay and cause a false-positive result.

There are several ways to clarify the diagnosis. First, phantom β-hCG can be demonstrated by a negative urine pregnancy test, but only if the patient's serum β-hCG level is significantly higher than the detection threshold of the urine test. Second, performing serial dilutions of the serum sample results in a proportional decrease in the β-hCG level if β-hCG is truly present; phantom β-hCG measurements will be unchanged. In addition, if phantom β-hCG is suspected, some specialized laboratories may be able to block the heterophilic antibodies. Lastly, a different β-hCG assay performed using an alternate method may accurately demonstrate the absence of true β-hCG (Cole, 1998; Olsen, 2001; Rotmensch, 2000).

QUIESCENT GESTATIONAL TROPHOBLASTIC DISEASE

Patients with persistent mild elevations (usually in the range of 50 mIU/mL or less) of true β-hCG may have a dormant premalignant condition if no tumor is identified by physical examination or imaging studies (Khanlian, 2003). In this instance, phantom β-hCG also should be conclusively excluded as a possibility. The low β-hCG titers may persist for months or years before disappearing. Chemotherapy and surgery usually have no effect. Hormonal contraception may be helpful in lowering titers to an undetectable level, but patients should be monitored closely because metastatic GTN may develop eventually (Khanlian, 2003; Kohorn, 2002).

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ANATOMY: INTRODUCTION

A gynecologic surgeon must be familiar with the anatomy of the female pelvis and lower abdominal wall. Over the past 20 years, the rote knowledge of pelvic anatomy has been complemented by a better understanding of the neuromuscular physiology that governs pelvic function. This chapter presents a broad overview of these relationships.

ANTERIOR ABDOMINAL WALL

The anterior abdominal wall provides core support to the human torso, confines abdominal viscera, and contributes muscular action for functions such as respiration and elimination. In gynecology, comprehensive knowledge of the layered structure of the anterior abdominal wall is needed to effectively enter the peritoneal cavity for surgery without neurovascular complications.

Skin

The term *Langer lines* describes the orientation of dermal fibers within the skin. In the anterior abdominal wall, they are arranged in a primarily transverse orientation. As a result, vertical skin incisions sustain more lateral tension and thus in general develop wider scars. In contrast, low transverse incisions, such as the Pfannenstiel, follow Langer lines and lead to superior cosmetic results.

Subcutaneous Layer

This layer of the anterior abdominal wall can be separated into a superficial, predominantly fatty layer known as *Camper fascia* and a deeper, more membranous layer known as *Scarpa fascia.* Camper and Scarpa fasciae are not discrete layers but represent a continuum of the subcutaneous tissue layer.

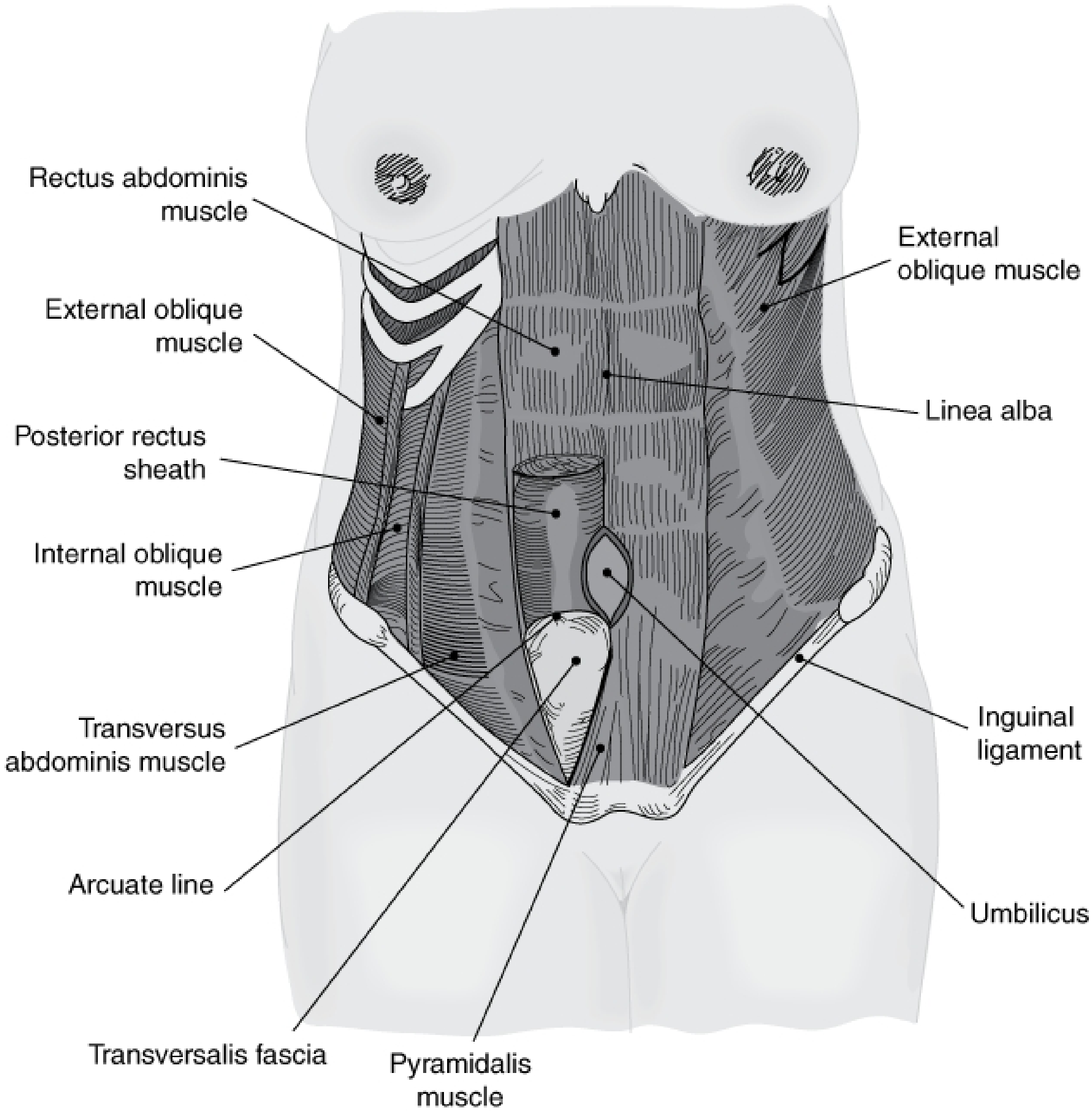
CLINICAL CORRELATION

Scarpa fascia is better developed in the lower abdomen and can be best identified in the lateral portions of a low transverse incision, just superficial to the rectus fascia. In contrast, this fascia is rarely recognized during midline incisions.

Rectus Sheath

The aponeuroses of the external oblique, internal oblique, and tranversus abdominis muscles (flank muscles) conjoin to create the *rectus sheath* (Fig. 38-1). In the lower abdomen, transition from the muscular to the aponeurotic component of the external oblique muscles takes place along a vertical line through the anterosuperior iliac spine. Transition from muscle to aponeurosis for the internal oblique and transversus abdominis takes place more medially. For this reason, muscle fibers of the internal oblique are often noted below the aponeurotic layer of the external oblique during low transverse incisions.

FIGURE 38-1

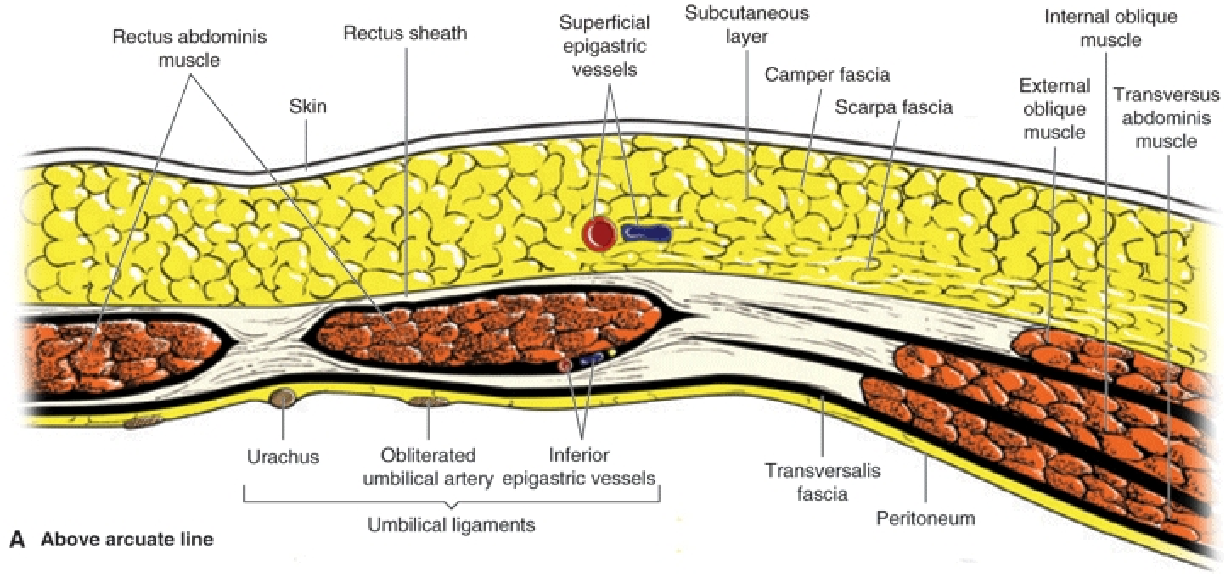


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

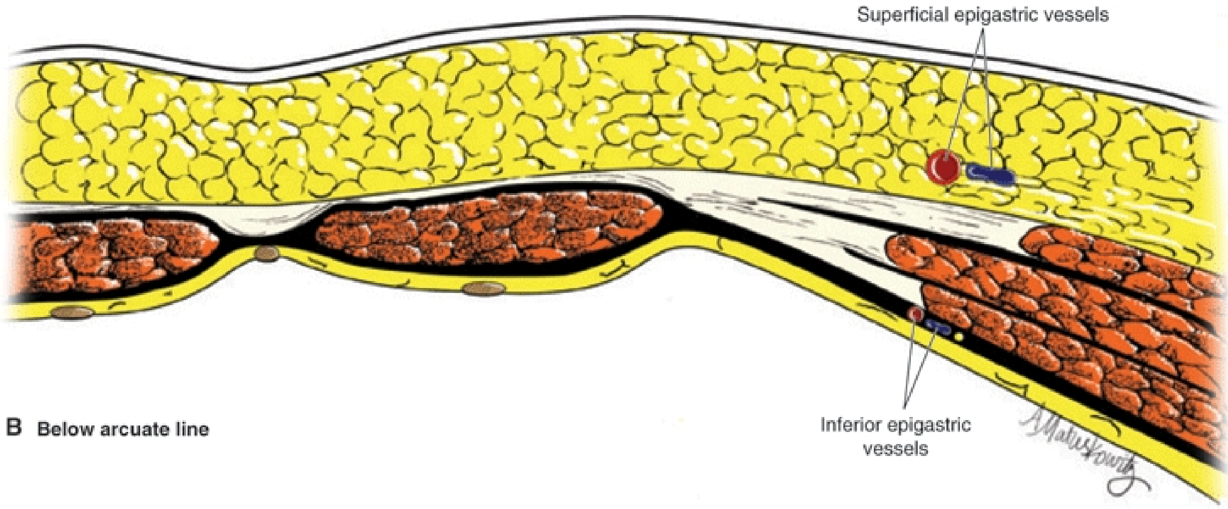
Muscles of the anterior abdominal wall. *(From Cundiff, 2002, with permission.)*

The anatomy of the rectus sheath above and below the *arcuate line* has significance to the surgeon (Fig. 38-2). This line defines the location at which the rectus sheath passes entirely anterior to the rectus muscles and typically lies midway between the umbilicus and pubic symphysis. Above the arcuate line, the rectus sheath lies anterior and posterior to the rectus muscles. At this level, the anterior rectus sheath is formed by the aponeurosis of the external oblique and the split aponeurosis of the internal oblique muscles. The posterior rectus sheath is formed by the split aponeurosis of the internal oblique muscle and the aponeurosis of the tranversus abdominis muscle. Below the arcuate line, all aponeurotic layers pass anterior to the rectus muscles. Thus, in the lower abdomen, the posterior surface of the rectus muscles is in direct contact with the transversalis fascia.

FIGURE 38-2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



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Tranverse sections of the anterior abdominal wall. **A.** Above the arcuate line. **B.** Below the arcuate line.

CLINICAL CORRELATION

In the lower abdomen, the aponeuroses of the internal oblique and tranversus abdominis muscles fuse. Therefore, only two layers are identified during low transverse fascial incisions (see Section 41-2, Pfannenstiel Incision).

Similar to the fibers of the skin, the flank muscles fibers are oriented primarily transversely. Therefore, suture lines in a vertical fascial incision are placed under more tension than those in a transverse incision. As a result, vertical fascial incisions are more prone to dehiscence and hernia formation.

Tranversalis Fascia

This thin layer of fibrous tissue lies between the inner surface of the transversus abdominis muscle and preperitoneal fat and thus serves as part of the general fascial layer that lines the abdominal cavity (see Fig. 38-2) (Memon, 1999). Inferiorly, the transversalis fascia blends with the periosteum of the symphysis pubis at a point lateral to the insertion of the rectus muscle.

CLINICAL CORRELATION

This fascia is best recognized as the layer bluntly or sharply dissected off the anterior surface of the bladder during entry into the abdominal cavity.

Peritoneum

The peritoneum that lines the inner surface of the abdominal walls is termed *parietal peritoneum.* In the anterior abdominal wall there are five vertical folds of parietal peritoneum that are raised by different structures. All five converge toward the umbilicus and are known as *umbilical ligaments.*

The single *median umbilical ligament* is formed by the urachus, an obliterated tube that extends from the apex of the bladder to the umbilicus. In fetal life, the urachus, or allantoic diverticulum, extends from the fetal hindgut to the umbilical cord. Transection of a patent urachus can result in extravasation of urine into the abdominal cavity. The paired *medial umbilical ligaments* are formed by the obliterated umbilical arteries that connected the internal iliac arteries to the umbilical cord in fetal life. Lastly, the paired *lateral umbilical ligaments* contain the inferior epigastric vessels.

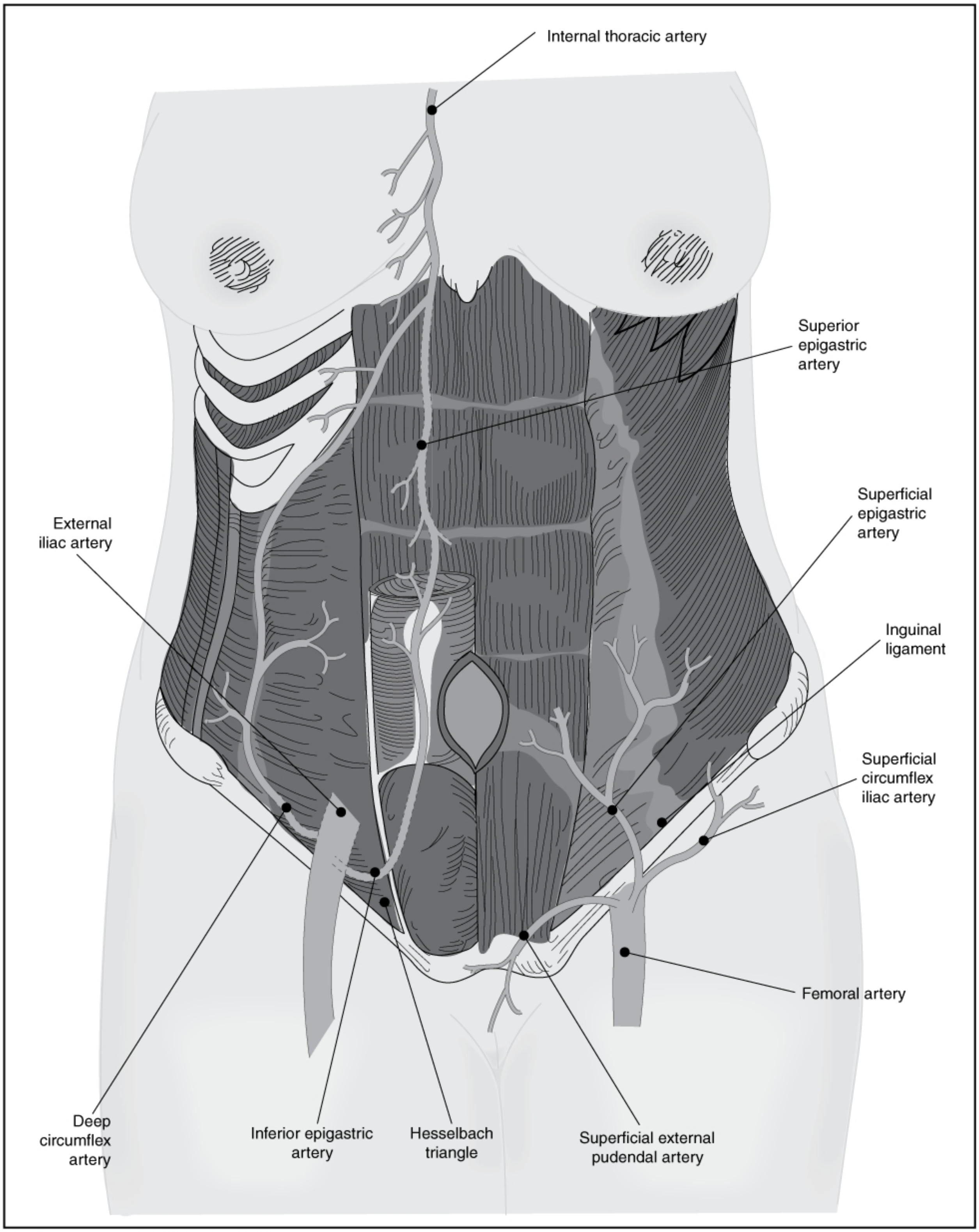
Blood Supply

Laceration of abdominal wall vessels can increase blood loss and risk of postoperative hematoma formation. Accordingly, familiarity with the origin and course of vessels that supply the anterior abdominal wall structures is critical when performing laparotomy and laparoscopy.

FEMORAL BRANCHES

The superficial epigastric, superficial circumflex iliac, and external pudendal arteries arise from the femoral artery just below the inguinal ligament in the region of the femoral triangle (Fig. 38-3). These vessels supply the skin and subcutaneous layers of the anterior abdominal wall and mons pubis. The *superficial epigastric vessels* course diagonally toward the umbilicus similar to the inferior "deep" epigastric vessels.

FIGURE 38-3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

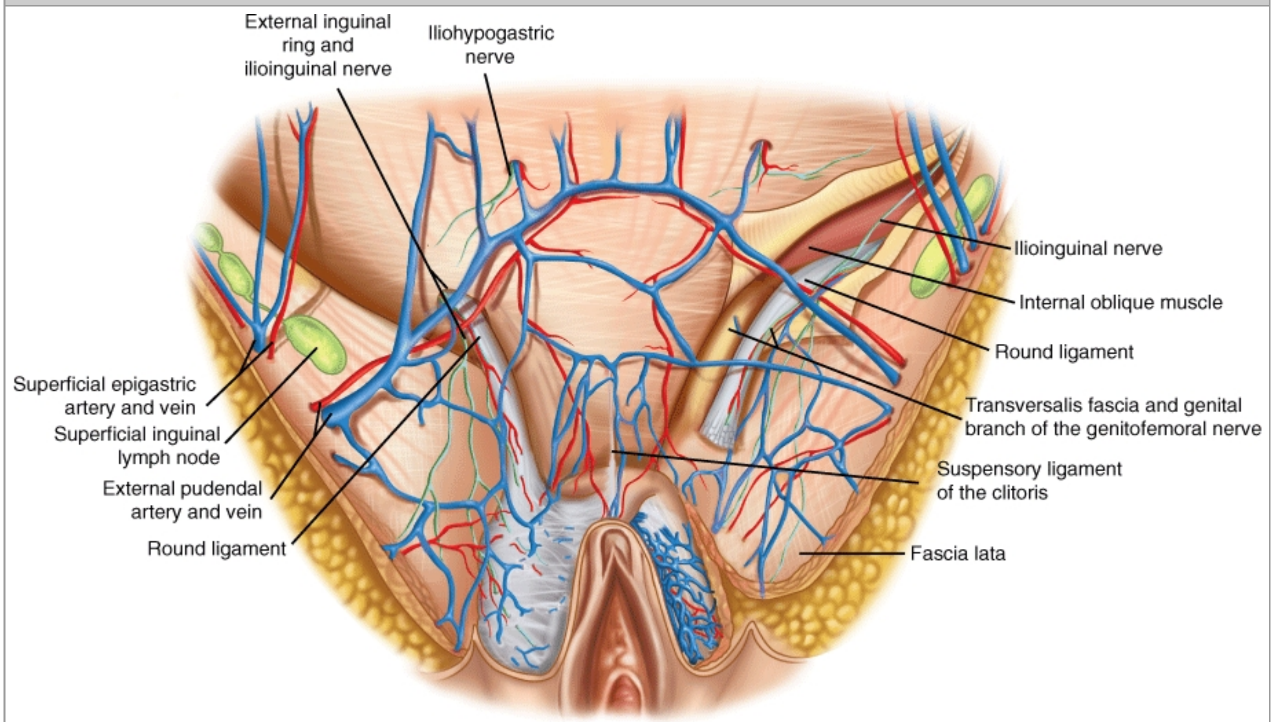
Vessels of the anterior abdominal wall. *(From Cundiff, 2002, with permission.)*

Clinical Correlation

During low transverse skin incisions, the superficial epigastric vessels usually can be identified halfway between the skin and the rectus fascia, several centimeters from the midline. During laparoscopic procedures in thin patients, these vessels can be identified by transillumination (see Section 41-28, Laparoscopy).

The external pudendal vessels form rich anastomoses with their contralateral equivalents and with other superficial branches. These anastomoses account for the extensive bleeding often encountered with incisions made in the mons pubis area (Fig. 38-4).

FIGURE 38-4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Pubic and inguinal regions. *(From Reiffenstuhl, 1975, with permission.)*

EXTERNAL ILIAC BRANCHES

The *inferior "deep" epigastric vessels* and *deep circumflex iliac vessels* are branches of the external iliac vessels (see Fig. 38-3). They supply the muscles and fascia of the anterior abdominal wall. The inferior epigastric vessels initially course lateral to and then posterior to the rectus muscles, which they supply. They then pass anterior to the posterior rectus sheath and course between the sheath and the rectus muscles. Near the umbilicus, the inferior epigastric vessels anastomose with the superior epigastric artery and veins, branches of the internal thoracic vessels.

Clinical Correlation

The inferior epigastric vessels also can be injured during accessory trocar placement with laparoscopy. Techniques to avoid their injury are discussed in Section 41-28, Laparoscopy. In addition, low transverse abdominal incisions that extend beyond the lateral margins of the rectus muscles can lead to vessel laceration with severe hemorrhage or anterior abdominal wall hematoma formation. These vessels should be identified and ligated when performing a Maylard incision (see Section 41-4, Maylard Incision).

Hesselbach triangle is the region in the anterior abdominal wall bounded inferiorly by the inguinal ligament, medially by the lateral border of the rectus muscles, and laterally by the inferior epigastric vessels (see Fig. 38-3). Direct hernias protrude through the abdominal wall in Hesselbach triangle, as opposed to indirect hernias that do so through the deep ring lying lateral to this triangle.

Nerve Supply

The anterior abdominal wall is innervated by the abdominal extensions of the intercostal nerves (T7-11), the subcostal nerve (T12), and the iliohypogastric and the ilioinguinal nerves (L1). The T10 dermatome approximates the level of the umbilicus.

The *iliohypogastric nerve* provides sensation to the skin over the suprapubic area. The *ilioinguinal nerve* supplies the skin of the lower abdominal wall and upper portion of the labia majora and medial portion of the thigh (see Fig. 38-4). These two nerves pass 2 to 3 cm medial to the anterosuperior iliac spine and course between the layers of the rectus sheath (see Fig. 38-2) (Whiteside, 2003).

CLINICAL CORRELATION

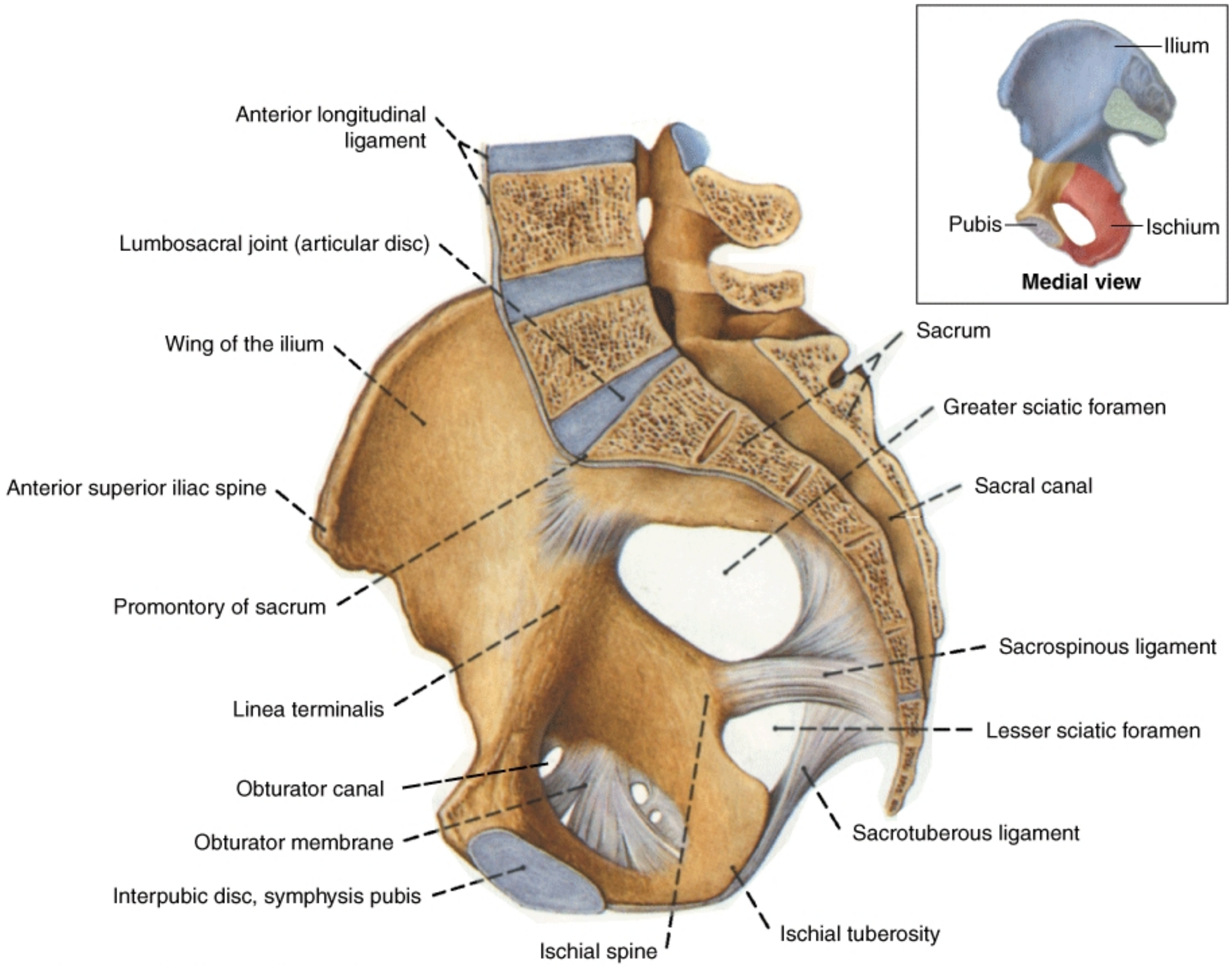
The ilioinguinal and iliohypogastric nerves can be severed during abdominal entry or entrapped during closure with low transverse incisions. This is especially true if incisions extend beyond the lateral borders of the rectus muscle. They also may be injured by placement of lower abdominal accessory trocars during laparoscopy. Most women with injury to these nerves present with loss of sensory function in the areas of distribution, however chronic pain can result (see Chap. 11, Neurologic).

PELVIC ANATOMY

Bony Pelvis and Pelvic Joints

The bony pelvis is comprised of (1) the two hip bones, termed the *inominate bones;* (2) the sacrum; and (3) the coccyx (Fig. 38-5). The innominate bones consist of the ilium, ischium, and pubis, which fuse at the acetabulum, a cup-shaped structure that articulates with the femoral head. The ilium articulates with the sacrum posteriorly at the sacroiliac joint, and the pubic bones articulate with each other anteriorly at the symphysis pubis. The s*acroiliac joint* is a synovial joint that connects the articular surfaces of the sacrum and ilium. This joint and its ligaments contribute significantly to the stability of the bony pelvis. The *symphysis pubis* is a cartilaginous joint that connects the articular surfaces of the pubic bones by way of a fibrocartilaginous disk. The ischial spines are clinically important bony prominences that project posteromedially from the medial surface of the ischium approximately at the level of the fifth sacral vertebra (S5).

FIGURE 38-5



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Hemisected female pelvis. *Inset:* Bones of the pelvis. *(From Clemente, 1997, and McKinley, 2006, with permission.)*

Pelvic Openings

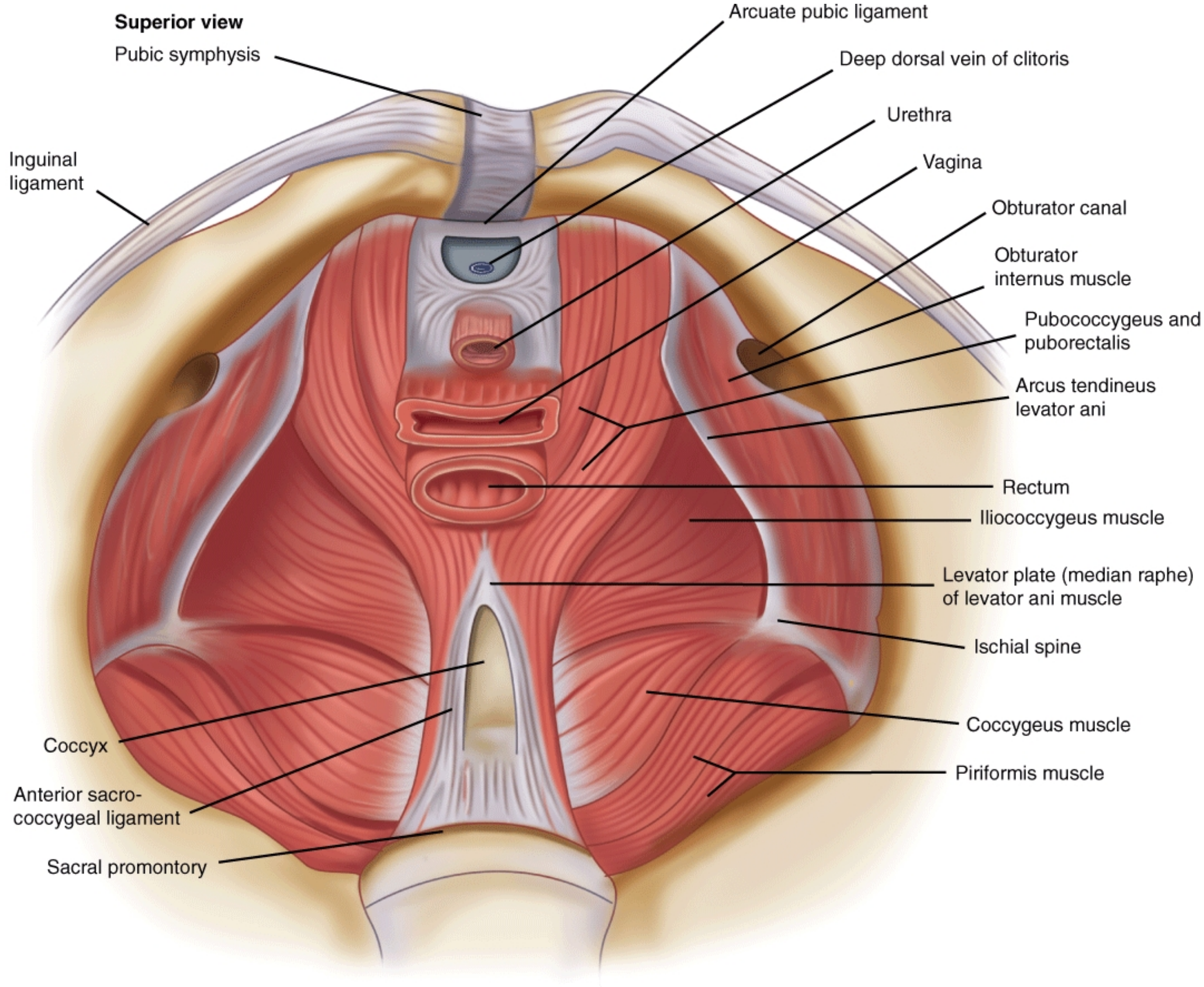
The posterior, lateral, and inferior walls of the pelvis have several openings through which many important structures pass. The large *obturator foramen* between the ischium and pubis is filled almost completely by the obturator membrane (see Fig. 38-5). In the superior portion of this membrane, a small aperture known as the *obturator canal* allows passage of the obturator neurovascular bundle into the medial (adductor) compartment of the thigh.

The posterolateral walls of the pelvis are not covered by bone. Instead, two important accessory ligaments, the sacrospinous and sacrotuberous, divide the greater and lesser sciatic notches of the ischium into the *greater sciatic foramen and lesser sciatic foramen* (see Fig. 38-5). The piriformis muscle, internal pudendal and inferior gluteal vessels, sciatic nerve, and other branches of the sacral nerve plexus pass through the greater sciatic foramen in close proximity to the ischial spines. The internal pudendal vessels, pudendal nerve, and obturator internus tendon pass through the lesser sciatic foramen.

Posteriorly, there are four pairs of pelvic sacral foramina. These allow passage of the anterior divisions of the first four sacral nerves and lateral sacral arteries and veins.

Lastly, the *urogenital hiatus* is the U-shaped opening in the pelvic floor muscles. Through it the urethra, vagina, and rectum pass (Fig. 38-6).

FIGURE 38-6



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Superior view of pelvic floor muscles. *(From Netter, 1989, with permission.)*

CLINICAL CORRELATION

Anatomic knowledge of the greater sciatic foramen area is critical to avoid neurovascular injury during sacrospinous fixation procedures and when administering pudendal nerve blockade. Weakening and opening of the urogenital hiatus from neuromuscular injury to pelvic floor muscles allows urogenital prolapse, as described below.

Ligaments

The term *ligament* is most often used to describe dense connective tissue that connects two bones. However, the ligaments of the pelvis are variable in composition and function. They range from tough connective tissue structures that support the bony pelvis and pelvic organs to smooth muscle and loose areolar tissue that add no significant support. *Of these the Sacrospinous ligament, sacrotuberous ligament,* and *anterior longitudinal ligament of the sacrum* consist of dense connective tissue that joins bony structures and contribute to the stability of the bony pelvis.

CLINICAL CORRELATION

The sacrospinous and anterior longitudinal ligaments serve as suture fixation sites in suspensory procedures used to correct pelvic

organ prolapse. The iliopectineal ligament, also termed *Cooper ligament,* is a thickening in the periosteum of the pubic bone that is often used to anchor sutures in retropubic bladder neck suspension procedures.

The round and broad ligaments consist of smooth muscle and loose areolar tissue, respectively. Although they connect the uterus and adnexa to the pelvic walls, they do not contribute to the support of these organs. In contrast, the cardinal and uterosacral ligaments do aid in pelvic organ support and are discussed later (Uterine Support).

Pelvic Wall Muscles and Fascia

MUSCLES

The posterior, lateral, and inferior walls of the pelvis are partially covered by striated muscles and their investing layers of fasciae (Fig. 38-6). The *piriformis muscle* arises from the anterior and lateral surfaces of the sacrum and partially fills the posterolateral pelvic walls. It exits the pelvis through the greater sciatic foramen, attaches to the greater trocanter of the femur, and functions as an external or lateral hip rotator. The *obturator internus muscle* partially fills the sidewalls of the pelvis. This muscle arises from the pelvic surfaces of the ilium and ischium, as well as from the obturator membrane. It exits the pelvis through the lesser sciatic foramen, attaches to the greater trochanter of the femur, and also functions as an external hip rotator.

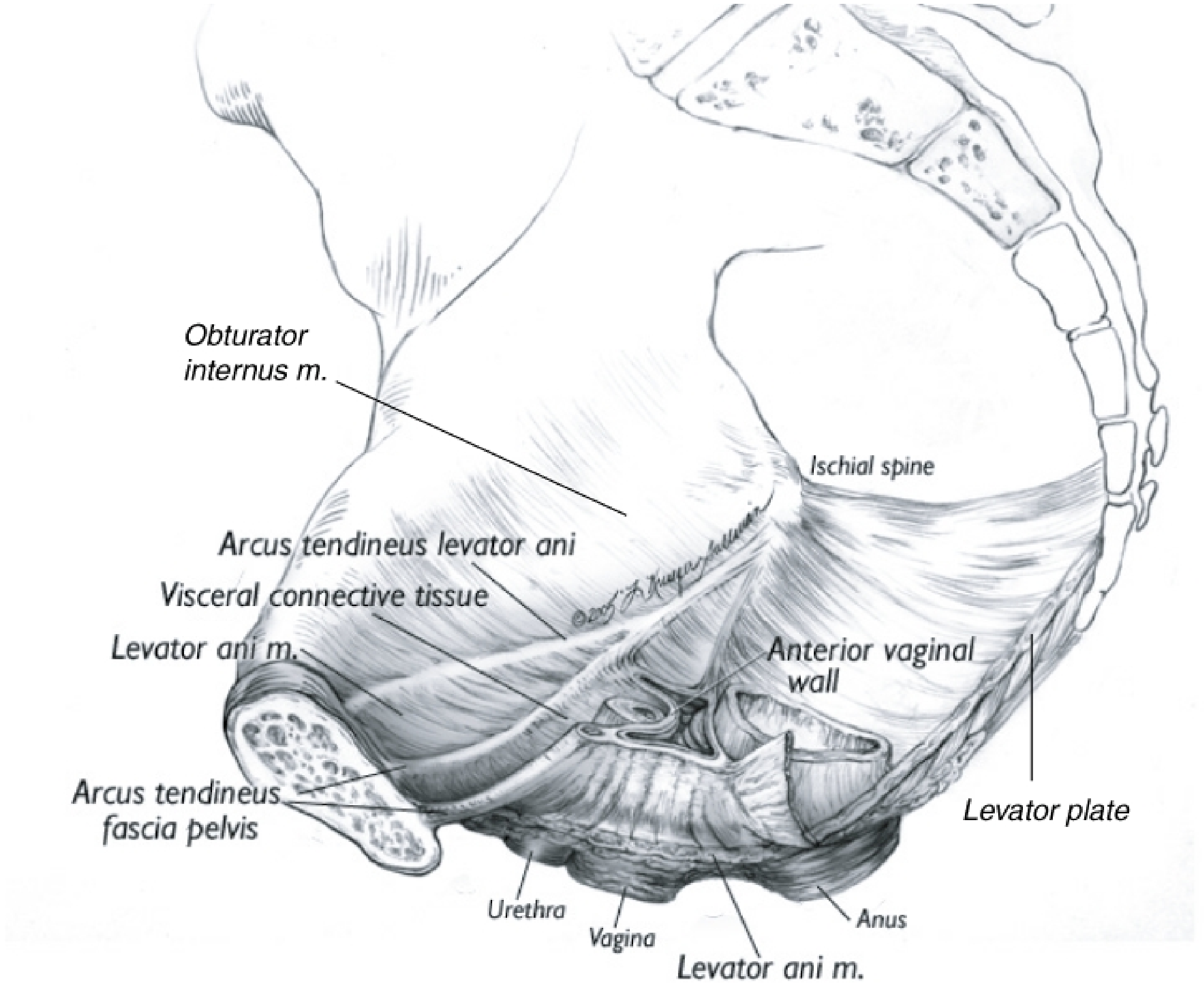
Clinical Correlation

Stretch injury to the piriformis muscle may cause persistent hip pain that can be confused with other hip or pelvic pathology.

FASCIA

The fascia that invests striated muscles is termed *parietal fascia* . Histologically, this tissue consists of regular arrangements of collagen. Pelvic parietal fascia provides muscle attachment to the bony pelvis and serves as anchoring points for visceral fascia, also termed *endopelvic fascia* . Shown in Figure 38-7 is the *arcus tendineus levator ani* , a condensation of fascia covering the medial surface of the obturator internus muscle. This structure serves as the point of origin for parts of the very important levator ani muscles. Also shown is the *arcus tendineus fascia pelvis* , a condensation of fascia covering the medial aspect of the obturator internus and levator ani muscles. It represents the lateral point of attachment of the anterior vaginal wall.

FIGURE 38-7



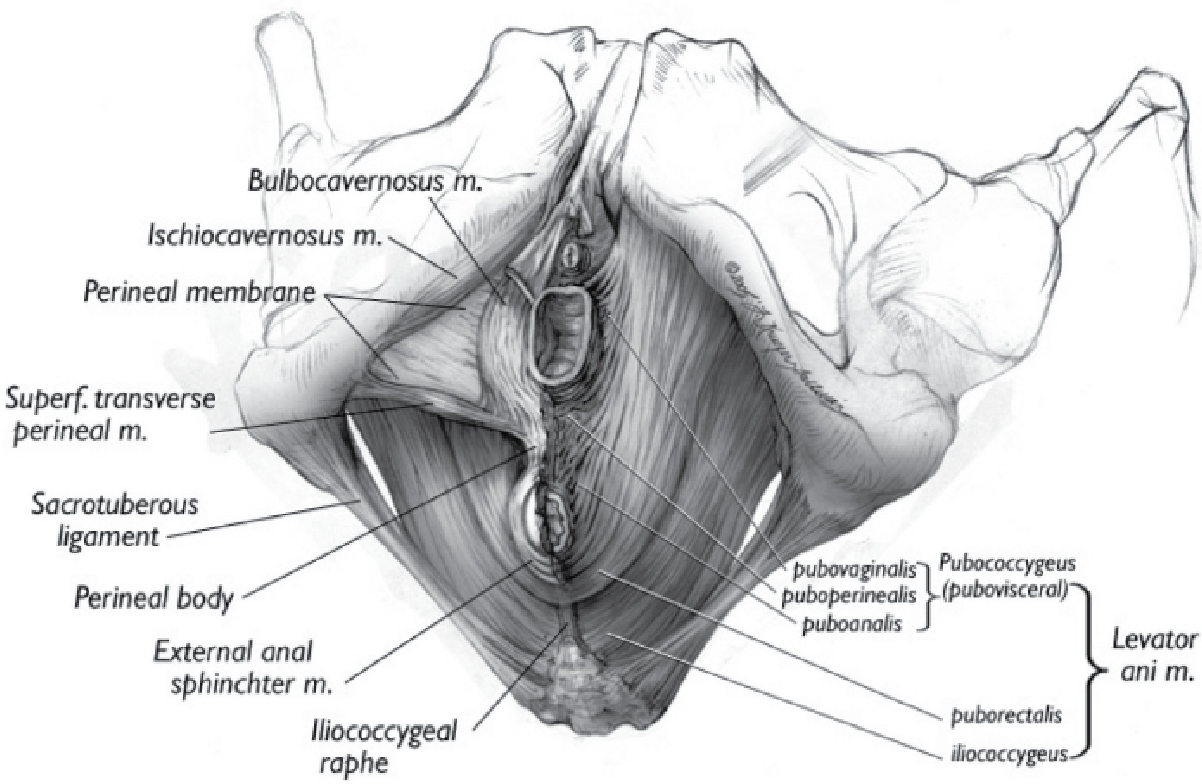
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

View of lateral pelvic sidewall.

Pelvic Floor

The muscles that span the pelvic floor are collectively known as the *pelvic diaphragm* (Fig. 38-8). This diaphragm consists of the levator ani and coccygeus muscles along with their superior and inferior investing layers of fasciae. Inferior to the pelvic diaphragm, the perineal membrane and perineal body also contribute to the pelvic floor.

FIGURE 38-8



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Inferior view of pelvic floor muscles.

LEVATOR ANI MUSCLES

This is the most important muscle in the pelvic floor and represents a critical component of pelvic organ support (see Figs. 38-6 and 38-8). Physiologically, normal levator ani muscles maintain a constant state of contraction. They provide a solid floor that supports the weight of the abdominopelvic contents against intra-abdominal forces.

The levator ani muscle is a complex unit that consists of several muscle components with different origins and insertions and therefore different functions. The *pubococcygeus, puborectalis,* and *iliococcygeus* are the three components of this muscle recognized in the *Terminologia Anatomica* (see Fig. 38-8). The pubococcygeus is further divided into the pubovaginalis, puboperinealis, and puboanalis muscles according to fiber attachments. Because of the significant attachments of the pubococcygeus to the walls of the pelvic viscera, the term *pubovisceral muscle* is used frequently to describe this portion of the levator ani muscle (Kerney, 2004, Lawson, 1974).

Pubococcygeus Muscle

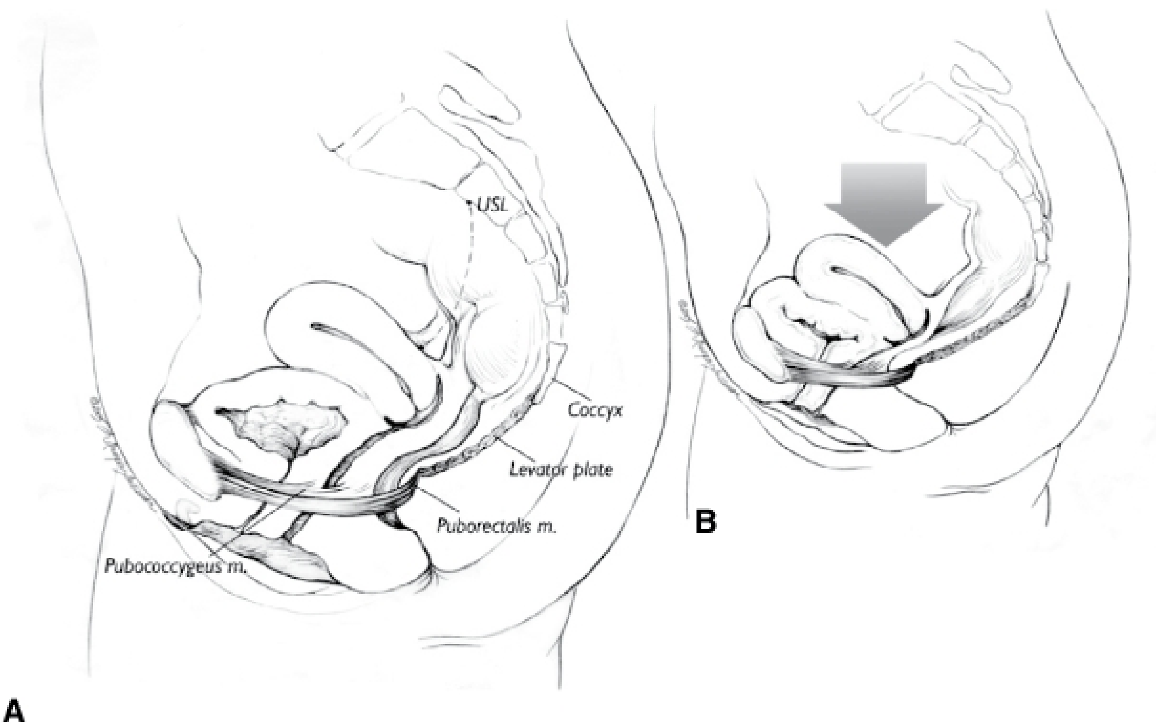
The anterior ends of the pubococcygeus (pubovisceral muscle) arise on either side from the inner surface of the pubic bone (see Fig. 38-8). The *pubovaginalis* refers to the medial fibers that attach to the lateral walls of the vagina. Although there are no direct attachments of the levator ani muscles to the urethra in females, those fibers of the muscle that attach to the vagina are responsible for elevating the urethra during a pelvic muscle contraction. Hence, these may contribute to urinary continence (DeLancey, 1990). The *puboperinealis* refers to the fibers that attach to the perineal body and draw this structure toward the pubic

symphysis. The *puboanalis* refers to the fibers that attach to the anus at the intersphincteric groove between the internal and external anal sphincters. These fibers elevate the anus and, along with the rest of the pubococcygeus and puborectalis fibers, keep the urogenital hiatus narrowed.

Puborectalis Muscle

The puborectalis represents the medial and inferior fibers of the levator ani muscle that arise on either side from the pubic bone and form a U-shaped sling behind the anorectal junction (Fig. 38-9). The action of the puborectalis draws the anorectal junction toward the pubis, contributing to the anorectal angle. This muscle is considered part of the anal sphincter complex and may contribute to maintenance of fecal continence (see Chap. 25, Anal Sphincter Complex).

FIGURE 38-9



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

A. Pelvic organs and pelvic floor muscles. **B.** With increasing intra-abdominal pressure, the muscles of the pelvic floor contract to support pelvic viscera.

Iliococcygeus Muscle

The iliococcygeus, the most posterior and thinnest part of the levator ani muscles, has a primarily supportive role. It arises laterally from the arcus tendineous levator ani and the ischial spines. Muscle fibers from one side join those from the opposite side at the coccyx and the iliococcygeal raphe, also termed the *anococcygeal raphe* (see Fig. 38-8).

The *levator plate* is the clinical term used to describe the region between the anus and the coccyx formed primarily by the insertion of the iliococcygeus muscles (see Figs. 38-7 and 38-9). This portion of the levator muscles forms a supportive shelf on which the rectum, upper vagina, and uterus rest.

In a woman with normal support, the levator plate lies almost parallel to the horizontal plane in the standing position (Berglas, 1953). One theory suggests that levator plate support prevents excessive tension or stretching of the connective tissue pelvic ligaments and faciae (Paramore, 1908). Accordingly, neuromuscular injury to the levator muscles may lead to eventual sagging or

vertical inclination of the levator plate and of the urogenital hiatus. Consequently, the vaginal axis becomes more vertical, and the cervix is oriented over the opened hiatus. The mechanical effect of this change is to increase strain on connective tissues that support the pelvic viscera. Increased urogenital hiatus size has been shown to correlate with increased severity of pelvic organ prolapse (DeLancey, 1998).

PELVIC FLOOR INNERVATION

The pelvic diaphragm muscles are innervated primarily by direct somatic efferents from the second through the fifth sacral nerve roots (S2-5). Traditionally, a dual innervation has been described. The pelvic or superior surface of the muscles is supplied by direct efferents from S2-5, which is the nerve to the levator ani muscle.

The perineal or inferior surface is supplied by branches of the pudendal nerve. This latter relationship has been challenged recently. It has been suggested that the pudendal nerve does not contribute to levator muscle innervation (Barber, 2002). Its branches do, however, innervate parts of the striated urethral sphincter and external anal sphincter muscles.

Separate innervation of the levator ani muscle and the striated urethral and anal sphincters may explain why some women develop pelvic organ prolapse and others develop urinary or fecal incontinence (Heit, 1996).

PELVIC CONNECTIVE TISSUE

Subperitoneal perivascular connective tissue and loose areolar tissue are found throughout the pelvis. This tissue connects the pelvic viscera to the pelvic walls and is termed *visceral* or *endopelvic fascia.* Recall that visceral fascia differs anatomically and histologically from parietal fascia, which invests most striated muscles (Table 38-1). Visceral fascia is intimately associated with the walls of the viscera and cannot be dissected in the same fashion as parietal fasciaâ€”for example, rectus fascia can be separated from its corresponding skeletal muscle.

Table 38-1 Differences between Visceral and Parietal Fascia of the Pelvic Floor Muscles

	Type of Fascia	
Characteristic	**Visceral or Endopelvic**	**Parietal**
Histologic	Loose arrangements of collagen, elastin, and adipose tissue	Organized collagen arrangements
Function	Allows expansion and contraction of invested structures	Provides muscle attachment to bones
Supportive role	Condensations lend some support to invested organs; encases neurovascular structures	Invests muscles to provide pelvic floor stability and function
Tensile strength	Elastic	Rigid

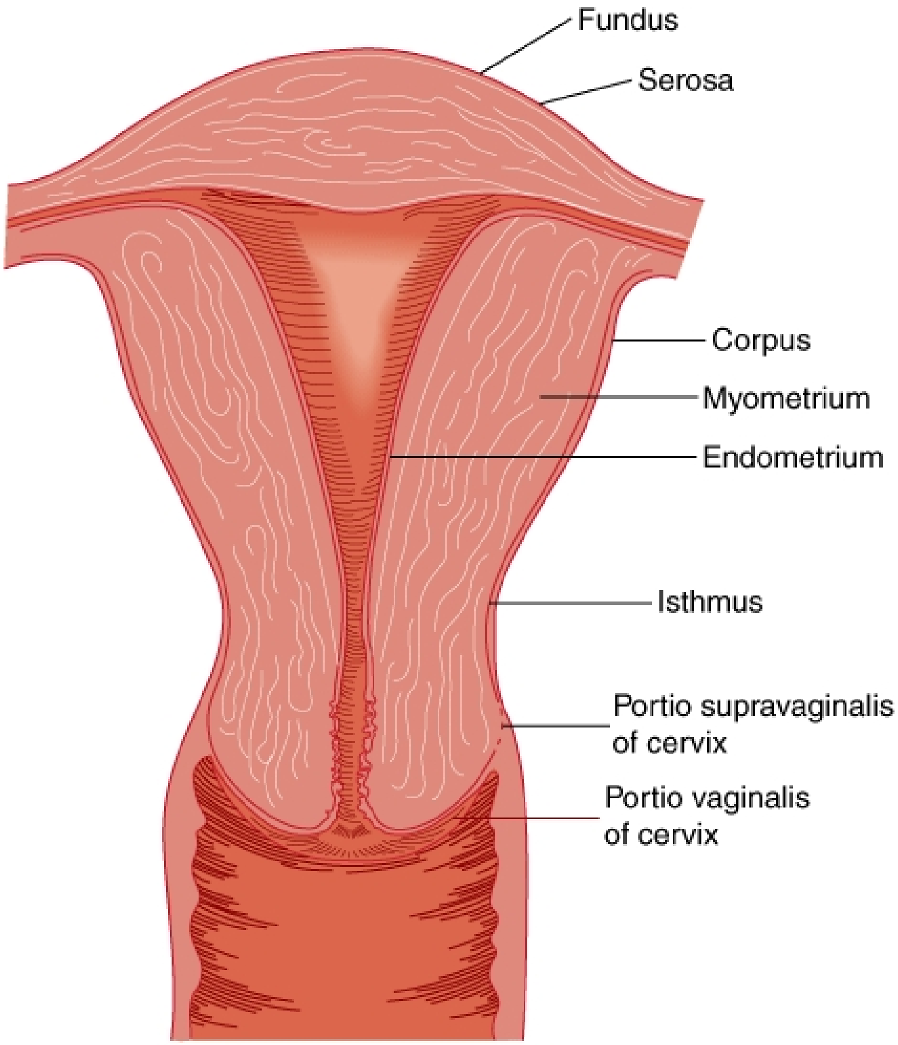
Condensations of visceral connective tissue that have assumed special supportive roles have been given different names. Some examples include the cardinal and uterosacral ligaments and the vesicovaginal and rectovaginal fasciae. These will be described further in sections below.

Pelvic Viscera

UTERUS

The uterus is a fibromuscular hollow organ situated between the bladder and the rectum. The uterus is divided structurally and functionally into two portions: an upper muscular body, the *corpus* , and a lower fibrous *cervix* (Fig. 38-10). The portion of the corpus that extends above the level of entry of the fallopian tubes into the endometrial cavity is known as the *fundus* .

FIGURE 38-10



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Uterine anatomy.

The shape, weight, and dimensions of the uterus vary according to parity and estrogen stimulation. Before menarche and after menopause, the corpus and cervix are approximately equal in size, but during the reproductive years, the uterine corpus is significantly larger. In the adult, nonpregnant woman, the uterus measures approximately 7 cm in length and 5 cm in width at the fundus and weighs 30 to 40 g. The embryologic development of the uterus and other pelvic viscera is discussed in Chapter 18.

Endometrium and Serosa

The uterus consists of an inner layer of mucosa called the *endometrium* that surrounds the endometrial cavity and a thick muscular wall known as the *myometrium.* The endometrium consists of columnar epithelium and specialized stroma. The superficial portion of the endometrium undergoes cyclic changes with the menstrual cycle (see Figs. 15-18 and 15-24).

The spiral arterioles located in the endometrium undergo hormonally mediated constriction or spasms that cause shedding of the superficial portion of this layer with each menstrual cycle. Because different arteries supply the deeper basal layer of the endometrium, this layer is preserved after the menstrual cycle and is the one responsible for regeneration of a new layer in the

subsequent cycle (see Fig. 8-2).

Peritoneal serosa overlays the outer wall except for the anterior portion of the cervix, which is covered by the bladder, and for the lateral portions of the corpus and cervix that attach to ligaments, as discussed below.

Cervix

The uterine cervix begins caudal to the uterine isthmus and is approximately 2 cm in length. The wall of the cervix consists primarily of fibrous tissue and a smaller amount (approximately 10 percent) of smooth muscle. The smooth muscle is found on the periphery of the cervical wall and serves as the point of attachment for the cardinal and uterosacral ligaments and for the fibromuscular walls of the vagina.

The attachments of the vaginal walls to the periphery of the cervix divides it vertically into a vaginal part known as the *portio vaginalis* and a supravaginal part known as the *portio supravaginalis.* The portio vaginalis is covered by nonkeratinizing squamous epithelium (see Fig. 38-10).

The endocervical canal is lined by columnar, mucus-secreting epithelium. The lower border of the canal, called the *external cervical* os, contains a transition from squamous epithelium of the portio vaginalis to columnar epithelium of the cervical canal (see Fig. 29-2). The exact location of this transition, termed the *squamocolumnar junction* and also called the *transformation zone* , varies depending on hormonal status. At the upper border of the endocervical canal is the internal cervical os, where the narrow cervical canal becomes continuous with the wider endometrial cavity.

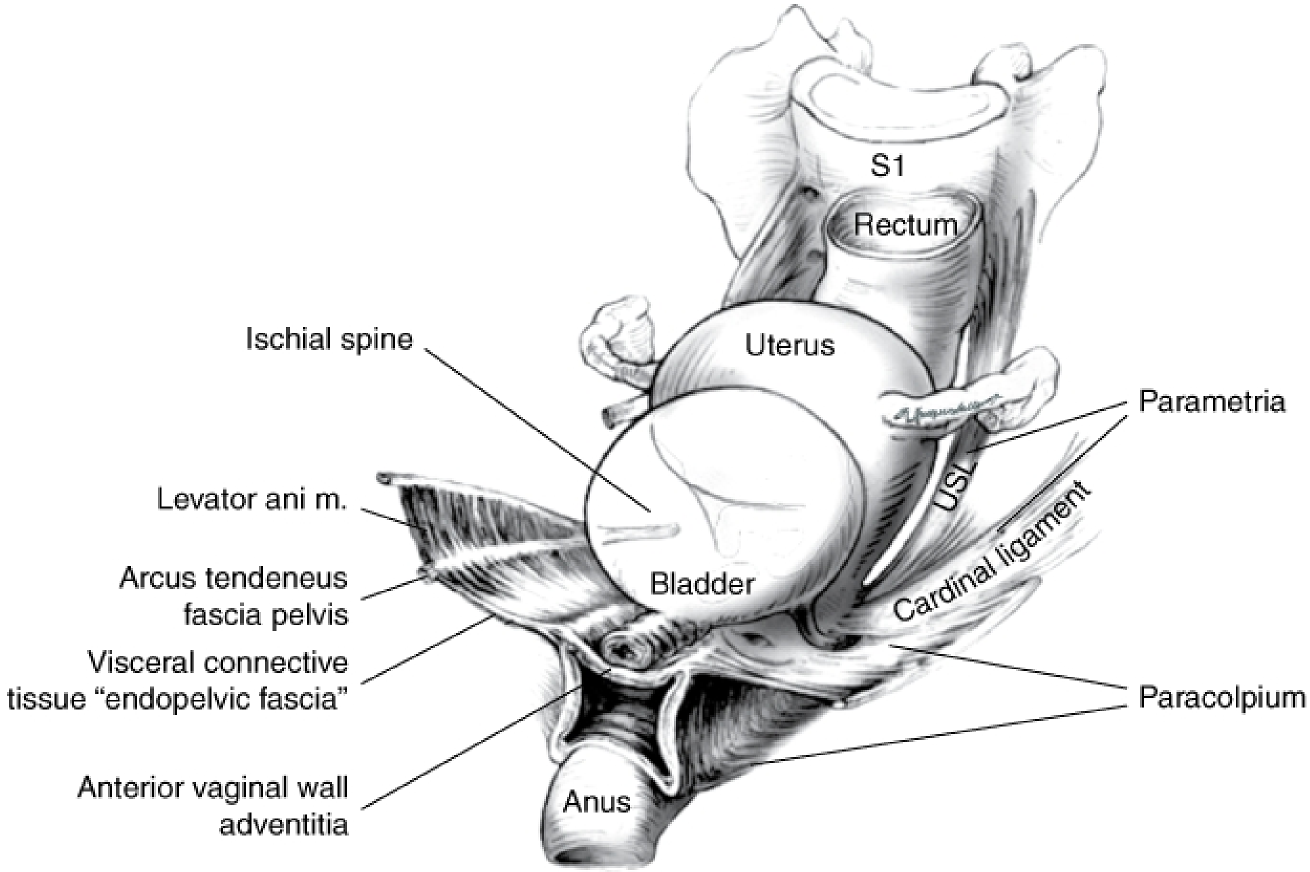
Clinical Correlation

Most squamous epithelial neoplasias originate at the squamocolumar junction. Thus, correct PAP smear preparation should sample cells from this junction, as discussed in Chapter 29, Cervical Cytology.

Uterine Support

The main support of the uterus and cervix is provided by the interaction between the levator ani muscles and the connective tissue that attaches the walls of the cervix to the pelvic walls. The connective tissue that attaches lateral to the uterus is called the *parametria.* It consists of what is known clinically as the *cardinal ligament* and *uterosacral ligament* (Figs. 38-11 and 38-12).

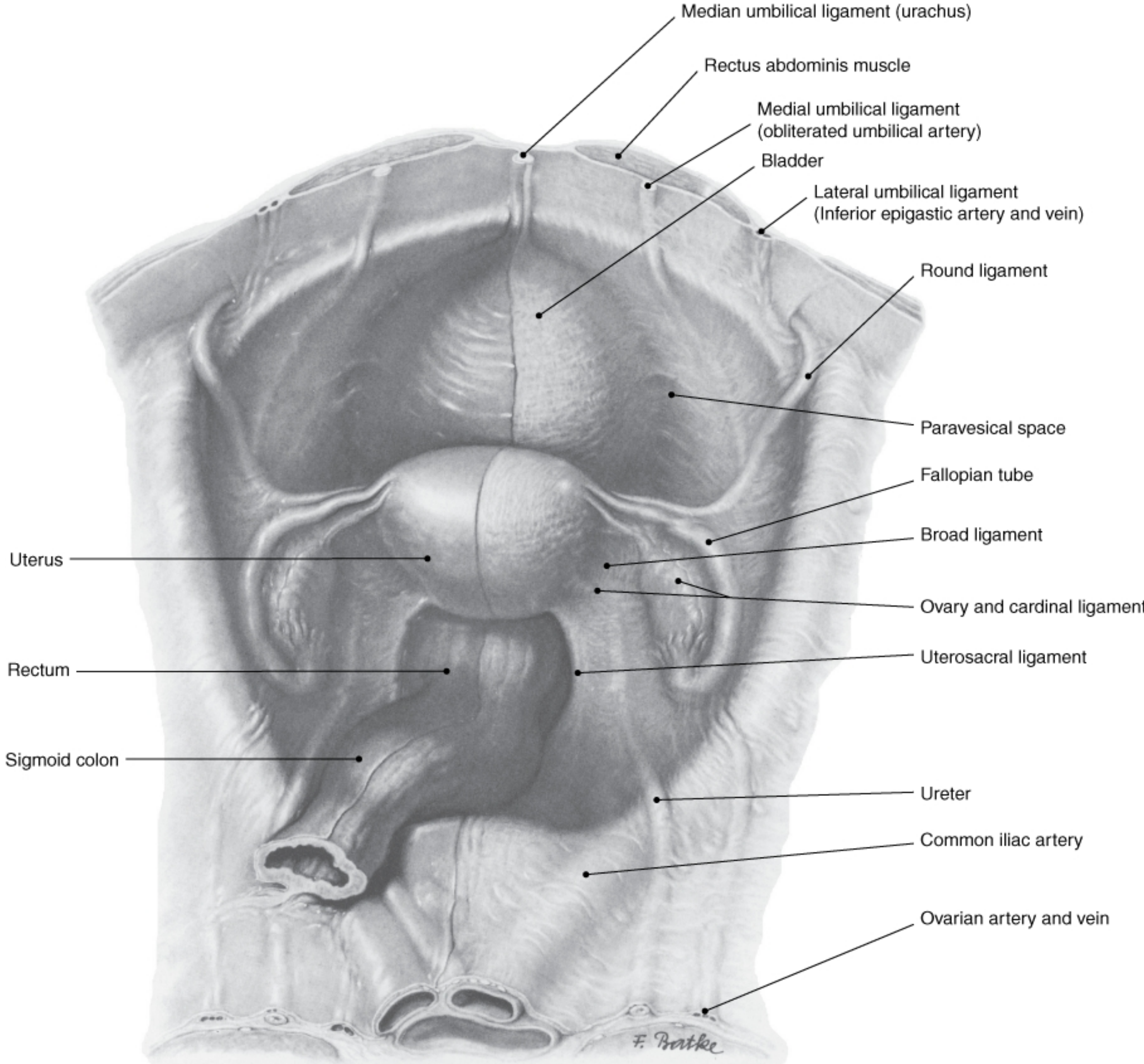
FIGURE 38-11



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Pelvic viscera and their support.

FIGURE 38-12



Major pelvic organs and associated anatomy. *(From Reiffenstuhl, 1975, with permission.)*

These ligaments are condensations of visceral connective tissue that have assumed special supportive roles. The cardinal ligaments, also termed *transverse cervical ligaments* or *Mackenrodt ligaments,* consist primarily of perivascular connective tissue (Range, 1964). They attach to the posterolateral pelvic walls near the origin of the internal iliac artery and surround the vessels supplying the uterus and vagina.

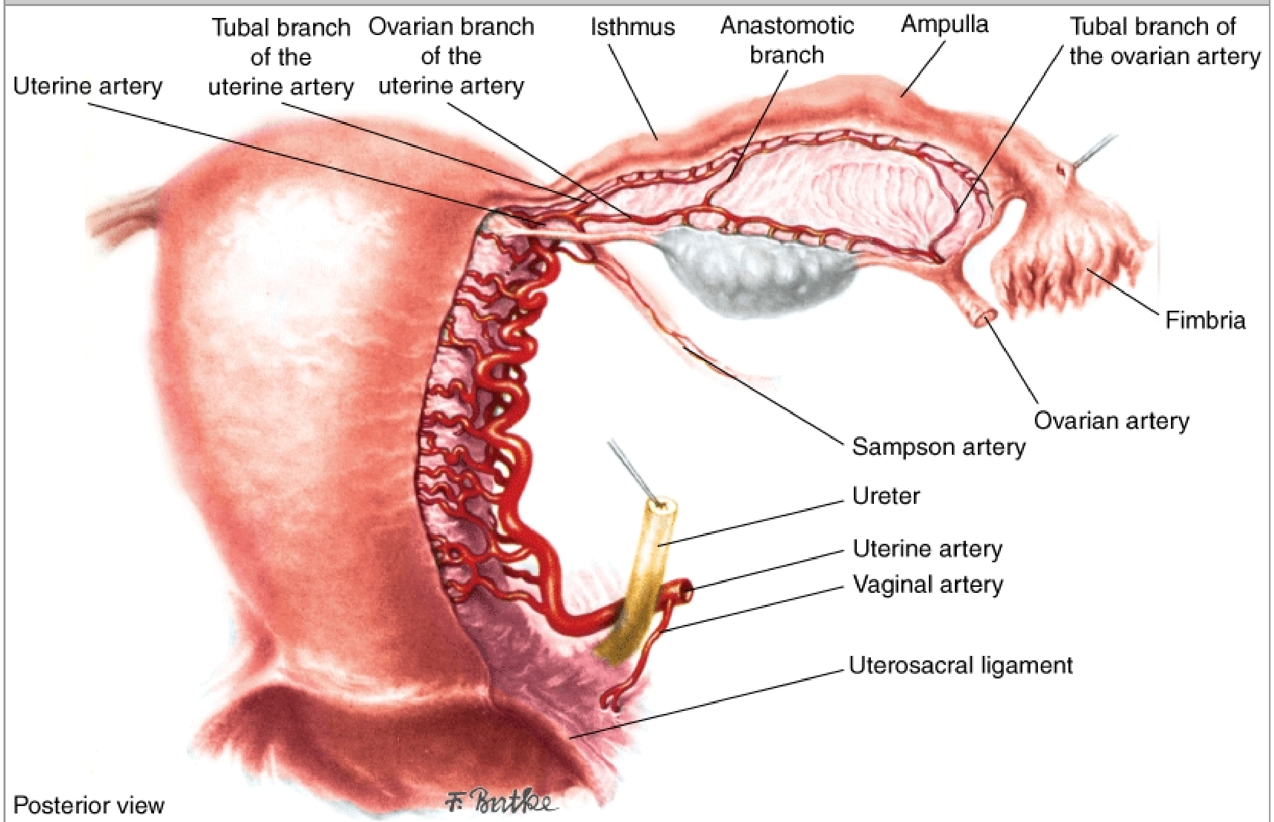
The uterosacral ligaments attach to a broad area of the sacrum posteriorly and form the lateral boundaries of the posterior cul-de-sac of Douglas (see Figs. 38-11 and 38-12). They consist primarily of smooth muscle and contain some of the pelvic autonomic nerves (Campbell, 1950). The parametria continues down along the vagina as the *paracolpium* , which is described below.

Round Ligaments

The *round ligaments* of the uterus are smooth muscle extensions of the uterine corpus and represent the homologue of the gubernaculum testis. The round ligaments arise from the lateral aspect of the corpus just below and anterior to the origin of the

fallopian tubes. They extend laterally to the pelvic sidewall (see Fig. 38-12). They enter the retroperitoneal space and pass lateral to the inferior epigastric vessels before entering the inguinal canal through the internal inguinal ring (see Fig. 38-4). After coursing through the inguinal canal, the round ligaments exit through the external inguinal ring to terminate in the subcutaneous tissue of the labia majora. The round ligaments do not contribute significantly to uterine support. They receive their blood supply from a small branch of the uterine or ovarian artery known as *Sampson artery* (Fig. 38-13).

FIGURE 38-13



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Uterine and adnexal blood supply. *(From Reiffenstuhl, 1975, with permission.)*

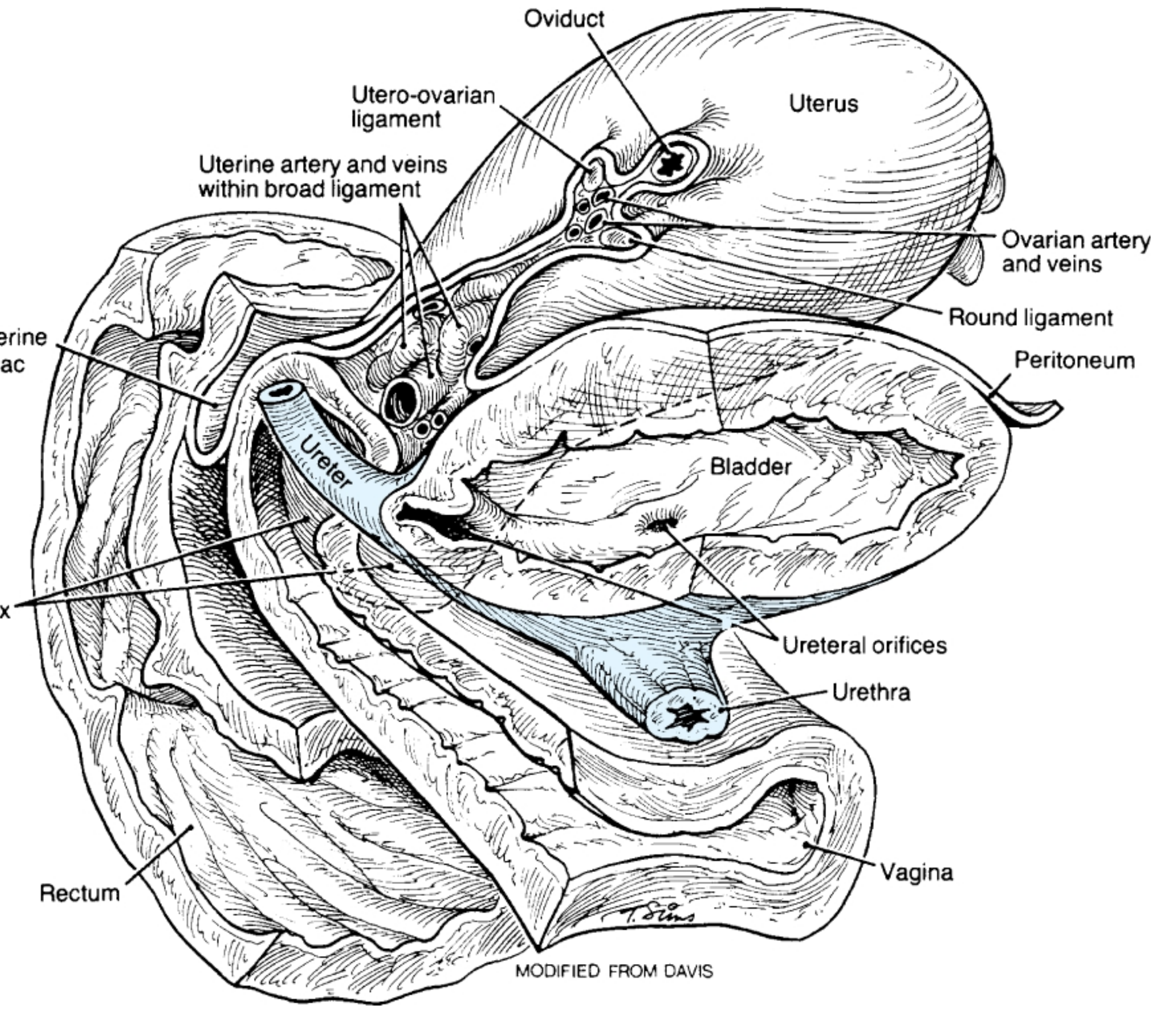
Clinical Correlation

The location of the round ligament anterior to the fallopian tube can assist a surgeon during tubal sterilization through a minilaparotomy incision. This may be especially true if pelvic adhesions limit tubal mobility and thus indentification of fimbria prior to tubal ligation.

Broad Ligaments

The broad ligaments are double layers of peritoneum that extend from the lateral walls of the uterus to the pelvic walls (Fig. 38-14). Within the upper portion of these two layers lie the fallopian tubes and the ovarian and round ligaments. The fallopian tubes, ovaries, and round ligaments each have their separate mesentery, called the *mesosalpinx, mesovarium,* and *mesoteres,* respectively, that carries nerves and vessels to these structures. At the lateral border of the fallopian tube and the ovary, the broad ligament ends where the infundibulopelvic ligament blends with the pelvic wall (see Fig. 38-12). The cardinal and uterosacral ligaments lie within the lower portion of the broad ligaments.

FIGURE 38-14

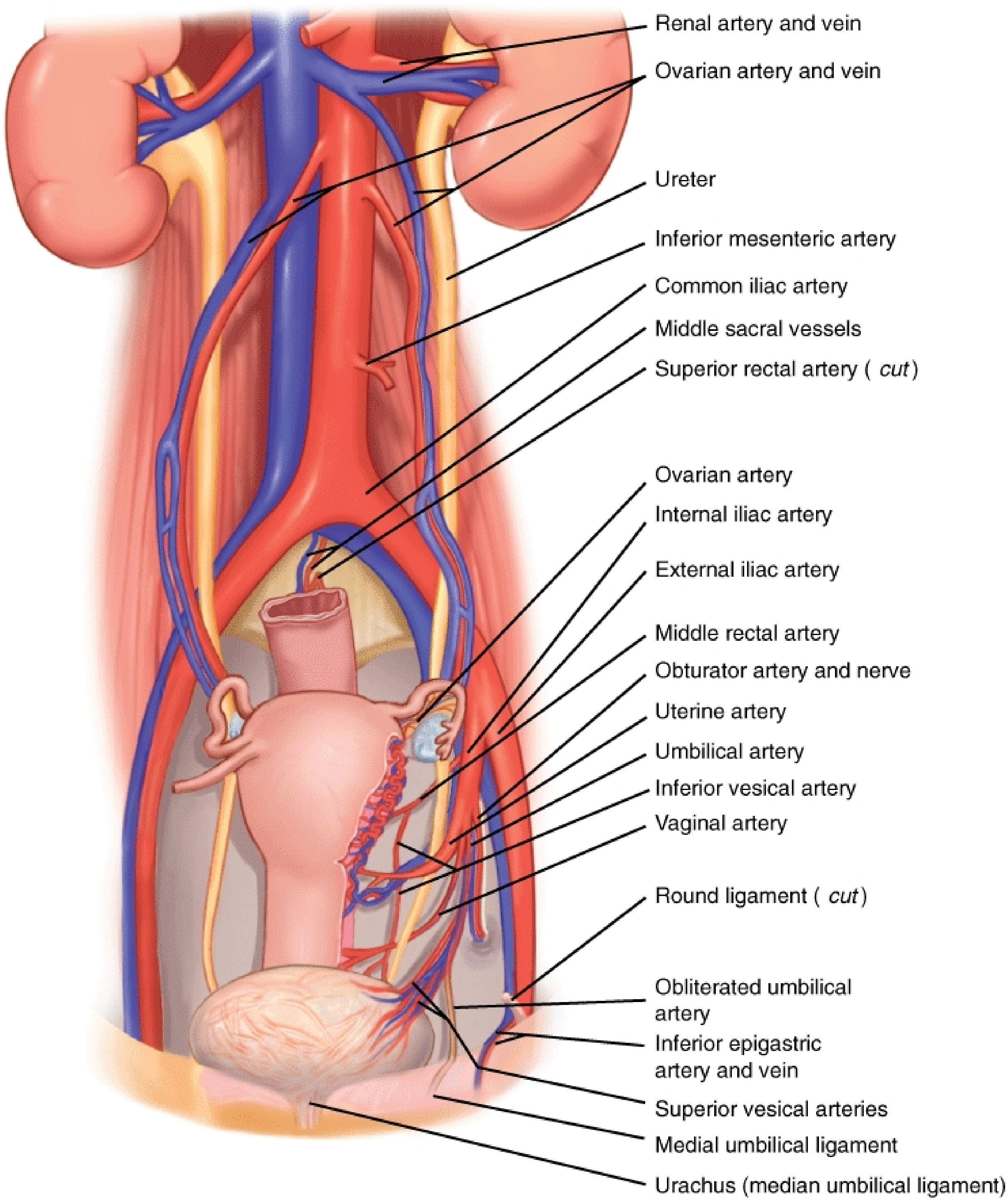


Sagittal section through the uterine end of the broad ligament. *(From Cunningham, 2005, with permission.)*

Uterine Blood Supply

The blood supply to the uterine corpus arises from the ascending branch of the *uterine artery* and from the medial or uterine branch of the *ovarian artery* (Fig. 38-15; see also Fig. 38-13). The uterine artery may originate directly from the internal iliac artery as an independent branch, or it may have a common origin with the internal pudendal or vaginal artery.

FIGURE 38-15



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Course of the ureter and blood supply to the pelvic organs. *(From Netter, 1989, with permission.)*

The uterine artery approaches the uterus in the area of transition between the corpus and the cervix known as the *uterine isthmus*

(see Figs. 38-10 and 38-13). In this area, the uterine artery courses over the ureter and provides a small branch to this structure. Several uterine veins course along the side of the artery and are variably found over or under the ureter. The uterine artery then divides into a larger ascending and a smaller descending branch that course along the side of the uterus and cervix. These vessels connect on the lateral border of the uterus and form an anastomotic arterial arcade that supplies the uterine walls.

The cervix is supplied by the descending or cervical branch of the uterine artery and by ascending branches of the vaginal artery.

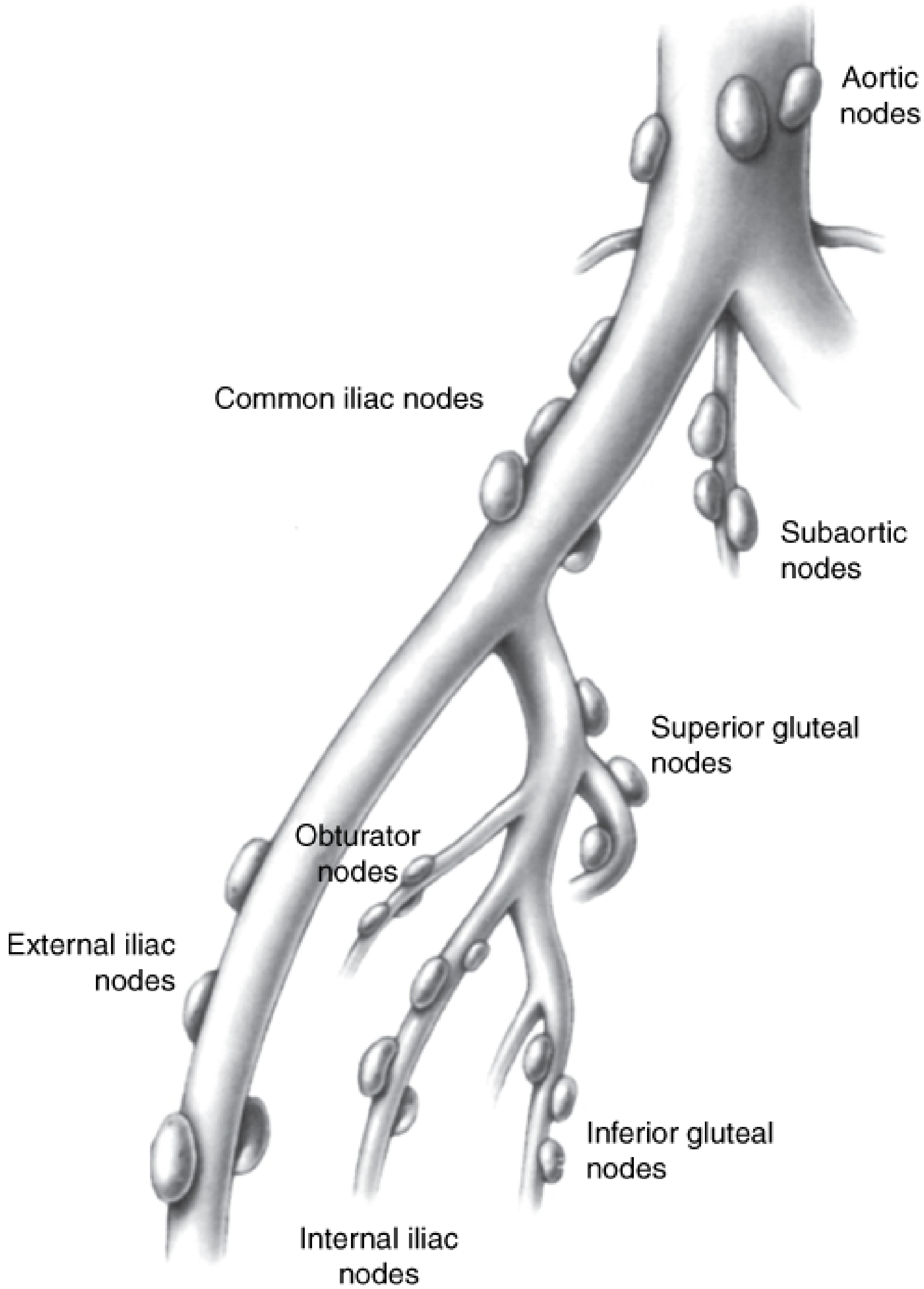
Clinical Correlation

The uterus receives dual blood supply from both ovarian and uterine vessels. For this reason, some surgeons during myomectomy place tourniquets at both the infundibulopelvic ligament and the uterine isthmus to decrease blood flow from the ovarian and uterine arteries, respectively.

Uterine Lymphatic Drainage

Lymphatic drainage of the uterus is primarily to the obturator and internal and external iliac nodes (Fig. 38-16). However, some lymphatic channels from the uterine corpus may pass along the round ligaments to the superficial inguinal nodes (see Fig. 38-4), and others may extend along the uterosacral ligaments to the lateral sacral nodes.

FIGURE 38-16



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Pelvic lymph nodes. *(From Plentyl, 1971, with permission.)*

Uterine Innervation

The uterus is innervated by fibers of the inferior hypogastric plexus, also known as *Frankenhauser ganglion,* that travel along the uterine arteries and are found in the connective tissue of the cardinal ligaments. Details of the organization of the pelvic visceral innervation are described later (Pelvic Innervation).

OVARIES AND FALLOPIAN TUBES

Ovaries

The ovaries and fallopian tubes constitute the uterine *adnexa* . The size and hormonal activity of the ovaries depend on age, time of the menstrual cycle, and exogenous hormonal suppression. During reproductive years, the ovaries measure 2.5 to 5 cm in length, 1.5 to 3 cm in thickness, and 0.7 to 1.5 cm in width.

Ovaries consist of an outer cortex and an inner medulla. Ovarian cortex is comprised of a specialized stroma punctuated with follicles, corpora lutea, and corpora albicantia. A single layer of mesothelial cells covers this cortex as a surface epithelium. The medullary portion of the ovary consists primarily of fibromuscular tissue and blood vessels. The medial portions of the ovaries are connected to the uterus by the *utero-ovarian ligament* (see Fig. 38-14). Laterally, each ovary is attached to the pelvic wall by an *infundibulopelvic ligament* , also termed *suspensory ligament of the ovary,* that contains the ovarian vessels and nerves (see Fig. 38-12).

Ovarian Blood Supply, Lymphatics, and Innervation

The blood supply to the ovaries comes from the ovarian arteries, which arise from the anterior surface of the abdominal aorta just below the origin of the renal arteries and from the ovarian branches of the uterine arteries (see Figs. 38-13 and 38-15). The ovarian veins follow the same retroperitoneal course as the arteries. The right ovarian vein drains into the inferior vena cava. However, the left ovarian vein drains into the left renal vein.

Lymphatic drainage of the ovaries follows the ovarian vessels to the lower abdominal aorta, where they drain into the para-aortic nodes (see Fig. 38-16).

Innervation to the ovaries are supplied by extensions of the renal plexus that course along the ovarian vessels in the infundibulopelvic ligament.

Fallopian Tubes

The fallopian tubes are tubular structures that measure 7 to 12 cm in length (see Fig. 38-13). Each tube has four identifiable portions. The *interstitial portion* passes through the body of the uterus at the region known as the *cornua.* The *isthmic portion* begins adjacent to the uterine corpus. It consists of a narrow lumen and a thick muscular wall. The *ampullary portion* is recognized as the lumen of the isthmic portion of the tube widens. In addition to a wider lumen, this segment has a more convoluted mucosa. The *fimbriated portion* is the distal continuation of the ampullary segment. The fimbriated end has many frond-like projections that provide a wide surface area for ovum pickup. The *fimbria ovarica* is the projection that is in contact with the ovary.

The ovarian artery runs along the hilum of the ovary and sends several branches through the mesosalpinx to supply the fallopian tubes (see Fig. 38-13). The venous plexus, lymphatic drainage, and nerve supply of the fallopian tubes follow a similar course to that of the ovaries.

VAGINA

The vagina is a hollow viscus whose shape is determined by the structures that surround it and by the attachments of its lateral walls to the pelvic walls, as described below. The distal portion of the vagina is constricted by the action of the levator ani muscles (see Fig. 38-8). Above the pelvic floor, the vaginal lumen is much more capacious and distensible. In the standing or anatomic position, the apex of the vagina is directed posteriorly toward the ischial spines, and the upper two thirds of the vaginal tube lie almost parallel to the horizontal plane of the floor (see Fig 38-9).

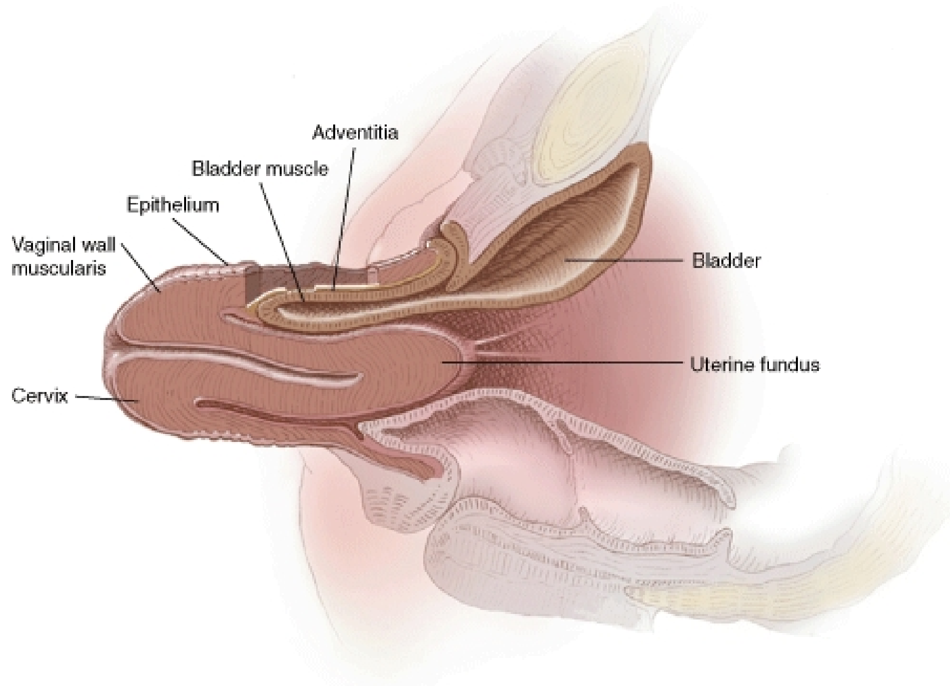
Although great variability in length of the vaginal walls is reported, the average length of the anterior vaginal wall is 7 cm, and that of the posterior wall is 9 cm. The shorter distance of the anterior vaginal wall results from the anterior position of the uterine cervix in most women. The recesses within the vaginal lumen in front of and behind the cervix are known as the *anterior fornix* and *posterior fornix,* respectively.

Vaginal Walls

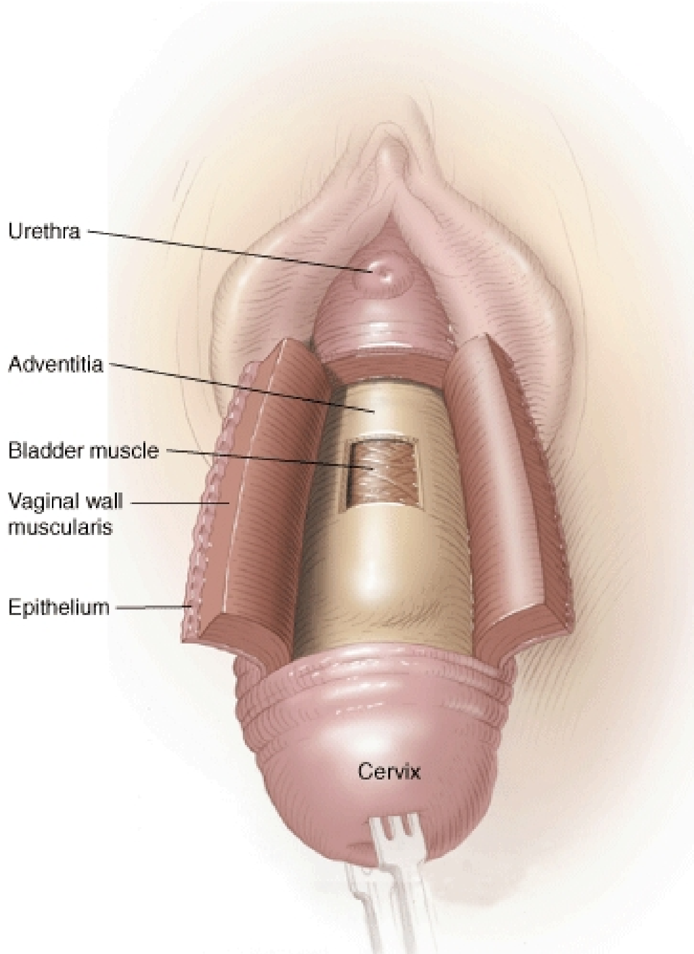
The walls of the vagina consist of three layers. First, adjacent to the lumen, there is a mucosal layer consisting of nonkeratinized squamous epithelium overlying a lamina propia. Below this epithelium, muscular layer is found and consists smooth muscle, collagen, and elastin. Lastly, an adventitial layer consisting of collagen and elastin lies beneath the muscularis (Fig. 38-17; see also

Fig. 24-5). (Weber, 1995, 1997).

FIGURE 38-17



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

A. Complete uterovaginal prolapse. Full-thickness portion of the anterior vaginal wall is resected to display vaginal wall layers. **B.** Anterior vaginal wall layers.

The vagina lies between the bladder and rectum and along with its connections to the pelvic walls provides support to these structures (see Fig. 38-14). The vagina is separated from the bladder and urethra anteriorly and the rectum posteriorly by the vaginal adventitia (see Figs. 38-11 and 38-17). The lateral continuation of the adventitial layer constitutes the paravaginal tissue that attaches the walls of the vagina to the pelvic walls, as described below. This tissue consists of loose areolar and fatty tissue containing blood vessels, lymphatics, and nerves.

The anterior fibromuscular vaginal wall and its paravaginal attachments represent the layer that supports the bladder and urethra. It is referred to clinically as *pubovesicocervical fascia* (see Fig. 38-11). Histologic studies have noted an absence of a true "fascial" layer between the vagina and the bladder and between the vagina and the rectum. Accordingly, some recommend that terms such as *pubocervical/pubovesical fascia* or *rectovaginal fascia* be abandoned. They propose that these are replaced by more accurate descriptive terms such as *vaginal muscularis* or *fibromuscular layer* of the anterior and posterior vaginal walls.

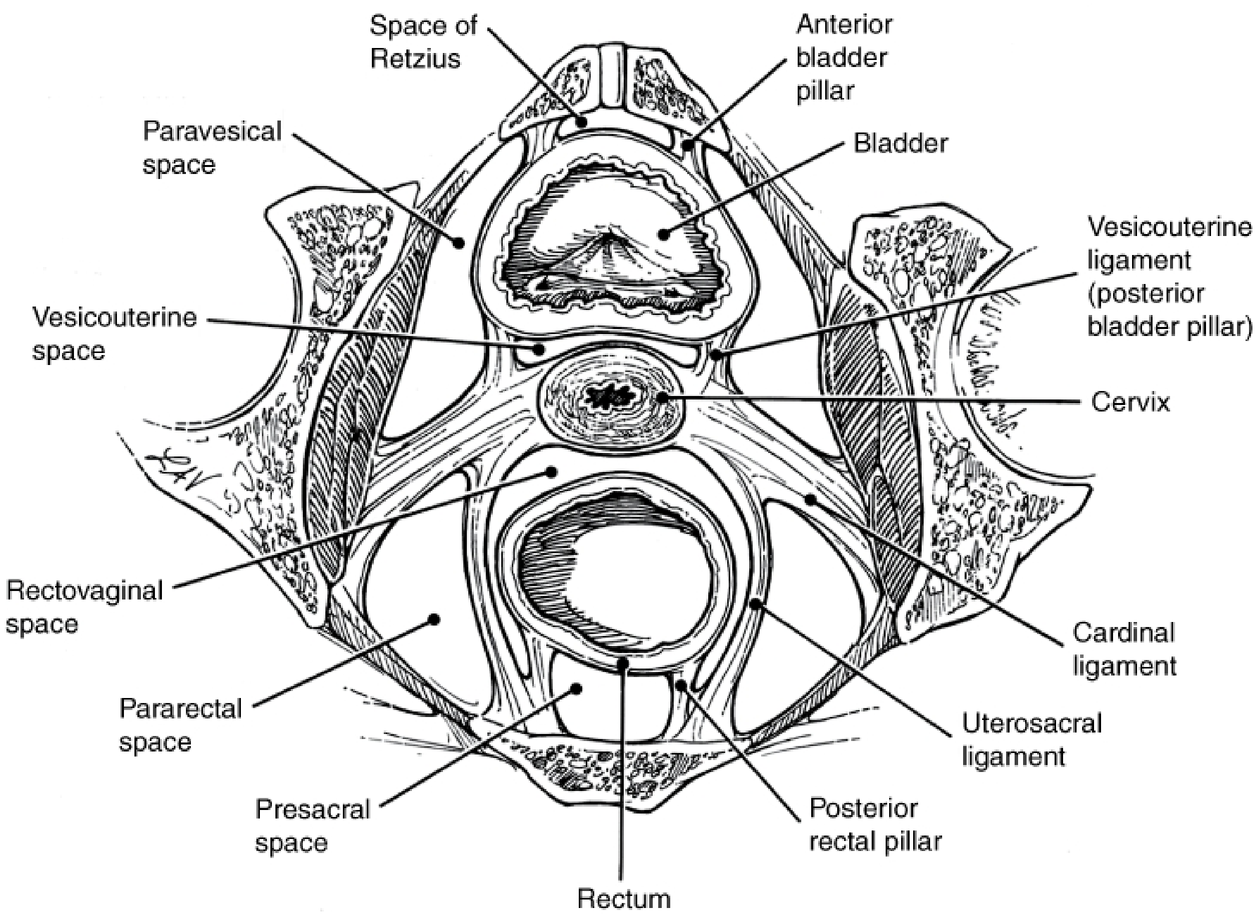
The lateral attachments of the posterior vaginal walls are to the fascia covering the medial surface of the levator ani muscles on the pelvic walls. The posterior wall and its connective tissue attachments to the sidewall support the rectum. This layer is known

clinically as the *rectovaginal fascia* or *fascia of Denonvilliers.* However, similar to microscopic findings of the anterior vaginal wall, histologic studies have failed to show a separate layer between the posterior wall of the vagina and the rectum except in the distal 3 to 4 cm, where the dense fibromuscular tissue of the perineal body separates these structure (DeLancey, 1999). Similar to surgical dissections in the anterior vaginal wall, posteriorly, the plane dissected surgically to separate the vaginal wall from rectum includes portions of the vaginal muscularis.

Vesicocervical and Vesicovaginal "Potential" Spaces

The *vesicocervical space* begins below the vesicouterine peritoneal fold or reflection, which represents the loose attachments of the peritoneum in the region of the anterior cul-de-sac (Fig. 38-18; see also Fig. 38-14). The vesicocervical space continues down as the *vesicovaginal space* , which extends to the junction of the proximal and middle thirds of the urethra. Below this point, the urethra and vagina fuse.

FIGURE 38-18



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Connective tissue and spaces of the pelvis. *(From Nichols, 2000, with permission.)*

Clinical Correlation

The vesicouterine peritoneal fold can be lifted and incised easily to create a bladder flap during an abdominal hysterectomy or cesarean delivery. The distance between the anterior cul-de-sac peritoneum and the anterior vaginal fornix is important during vaginal hysterectomies. This spans several centimeters. Therefore, prior to entering the peritoneal cavity, proper identification and sharp dissection of the loose connective tissue that lies within the vesicovaginal and vesicocervical spaces are necessary (see

Section 41-20, Vaginal Hysterectomy).

Rectovaginal Space

This is adjacent to the posterior surface of the vagina. It extends from the cul-de-sac of Douglas down to the superior border of the perineal body, which extends 2 to 3 cm above the hymeneal ring (see Figs. 38-14 and 38-18). *Rectal pillars* are fibers of the cardinalâ€"uterosacral ligament complex that extend down from the cervix and attach to the upper portion of the posterior vaginal wall. These fibers connect the vagina to the lateral walls of the rectum and to the sacrum and separate the midline rectovaginal space from the pararectal space.

Clinical Correlation

The rectovaginal space contains loose areolar tissue and is opened easily with finger dissection during abdominal surgery. During vaginal suspension procedures, perforation of the rectal pillar fibers allows access to the sacrospinous ligaments used in vaginal suspension procedures (see Section 41-19, Hysterectomy).

The posterior cul-de-sac peritoneum extends down the posterior vaginal wall 2 to 3 cm inferior to the posterior vaginal fornix (Kuhn, 1982). Thus, posterior entry into the peritoneal cavity during vaginal surgery is simplified. Posterior entry is done readily by incising the vaginal wall in the area of the posterior fornix (see Section 41-20, Vaginal Hysterectomy).

Vaginal Support

The main support of the vagina is provided by the interaction between the levator ani muscles and the connective tissue that attaches the lateral walls of the vagina to the pelvic walls. Although the visceral connective tissue in the pelvis is continuous and interdependent, DeLancey (1992) has described three levels of vaginal connective tissue support that help to explain various clinical manifestations of pelvic support dysfunction.

Upper Vaginal Support

The parametria continues down the vagina as the paracolpium (see Fig. 38-11). This tissue attaches the upper vagina to the pelvic wall, suspending it over the pelvic floor. These attachments are also known as *level I support* or the *suspensory axis* . They provide connective tissue support to the vaginal apex after hysterectomy. In the standing position, level I support fibers are vertically oriented. Clinical manifestations of level I support defects include posthysterectomy vaginal vault prolapse.

Midvaginal Support

The lateral walls of the midportion of the vagina are attached to the pelvic walls on each side by visceral connective tissue known as *endopelvic fascia.* These lateral attachments of the vaginal walls blend into the arcus tendineus fascia pelvis and the medial aspect of the levator ani muscles. In doing so, these lateral attachments create the anterior and posterior lateral vaginal sulci. These sulci run along the vaginal sidewalls and give the vagina an H shape when viewed in cross section (see Fig. 38-11). The *arcus tendineous fascia pelvis* is a condensation of fascia covering the medial aspect of the obturator internus and levator ani muscles (see Fig. 38-7). It spans from the inner surface of the pubic bones to the ischial spines. Attachment of the anterior vaginal wall to the levator ani muscles is responsible for the bladder neck elevation noted with cough or Valsalva (see Fig. 38-8). Therefore, these attachments may have significance for stress urinary continence. The midvaginal attachments are referred to as *level II support* or the *attachment axis.* Clinical manifestations of level II support defects include anterior and posterior vaginal wall prolapse and stress urinary incontinence.

Distal Vaginal Support

The distal third of the vagina is attached directly to its surrounding structures (see Fig. 38-8). Anteriorly, the vagina is fused with the urethra, laterally it attaches to the pubovaginalis muscle and perineal membrane, and posteriorly it attaches to the perineal body. These vaginal attachments are referred to as *level III support* or the *fusion axis.* They are considered the strongest of the vaginal support components. Failure of this level of support can result in distal rectoceles or perineal descent. Anal incontinence also may result if the perineal body is absent, as may follow obstetric trauma.

Vaginal Blood Supply, Lymphatics, and Innervation

The main blood supply to the vagina arises from the descending or cervical branch of the uterine artery and from the vaginal artery, a branch of the internal iliac (see Fig. 38-15). These vessels form an anastomic arcade along the lateral sides of the vagina at the level of the vaginal sulci. They anastomose with the contralateral vessels on the anterior and posterior walls of the vagina. Additionally, the middle rectal artery from the internal iliac contributes to supply the posterior vaginal wall. The distal walls of the vagina also receive contributions from the internal pudendal artery.

Lymphatic drainage of the upper two thirds of the vagina is similar to that of the uterus, as described earlier. The distal part of the vagina drains with the vulvar lymphatics to the inguinal nodes. A more detailed description of the vulvar lymphatics is presented in the vulva and perineum section of this chapter.

The vagina receives its nerve supply from the inferior extensions of the uterovaginal plexus, a component of the inferior hypogastric or pelvic plexus (Inferior Hypogastric Plexus).

LOWER URINARY TRACT STRUCTURES

Bladder

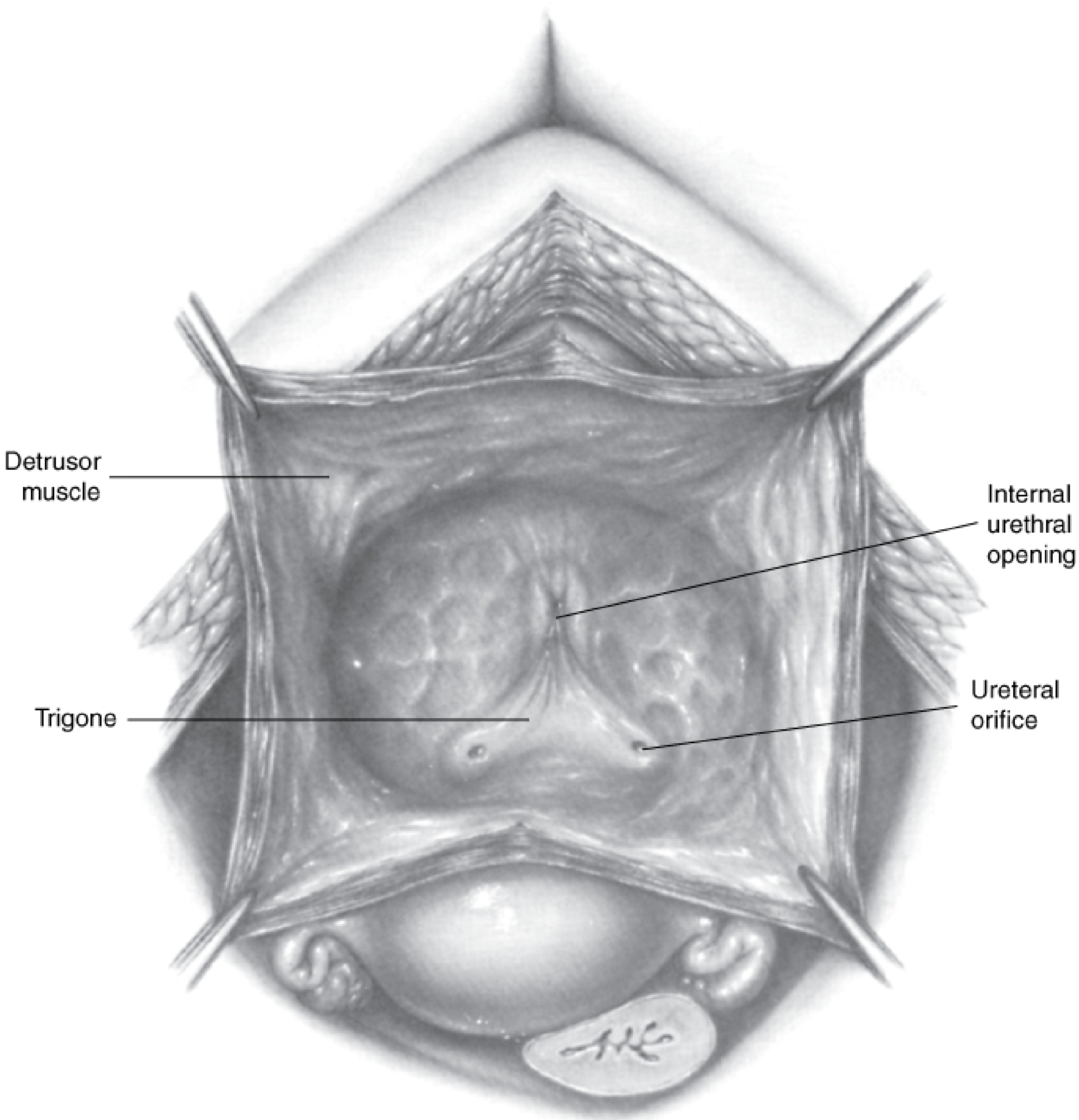
The bladder is a hollow organ that allows storage and evacuation of urine (see Fig. 38-14). Anteriorly, the bladder rests against the anterior abdominal wall, and posteriorly, it rests against the vagina and cervix. Inferiorly and laterally, the bladder is in contact with the inner surface of the pubic bones. In these areas, the bladder is devoid of peritoneal covering. The reflection of the bladder onto the abdominal wall is triangular in shape. The apex of this triangle is continuous with the median umbilical ligament (see Fig. 38-12).

Clinical Correlation

Because the apex of the bladder is highest in the midline, this is the area where bladder injury is most likely to result during peritoneal entry.

The bladder wall consists of coarse bundles of smooth muscle known as the *detrusor muscle* , which extends into the upper part of the urethra (Fig. 38-19). Although separate layers of the detrusor are described, they are not as well defined as the layers of other viscous structures, such as the bowel or the ureter (see Fig. 23-2). The innermost layer of the bladder wall is plexiform and can be seen from the pattern of trabeculations noted during cystoscopy. The mucosa of the bladder consists of transitional epithelium.

FIGURE 38-19



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Dome of the bladder is opened to display trigone anatomy and bladder wall muscle. *(From Thompson, 1997, with permission.)*

The bladder can be divided into a dome and a base approximately at the level of the ureteral orifices. The dome is thin-walled and distensible, whereas the base has a thicker wall that undergoes less distention during filling. The bladder base consists of the vesical trigone and the detrusor loops. These loops are two U-shaped bands of fibers found at the vesical neck, the area where the urethra enters the bladder wall (see Fig. 38-19).

The blood supply to the bladder arises from the superior and inferior vesical arteries. The superior vesical arteries are branches of

the patent portion of the umbilical artery. The inferior vesical artery, when present, arises from either the internal pudendal or the vaginal artery.

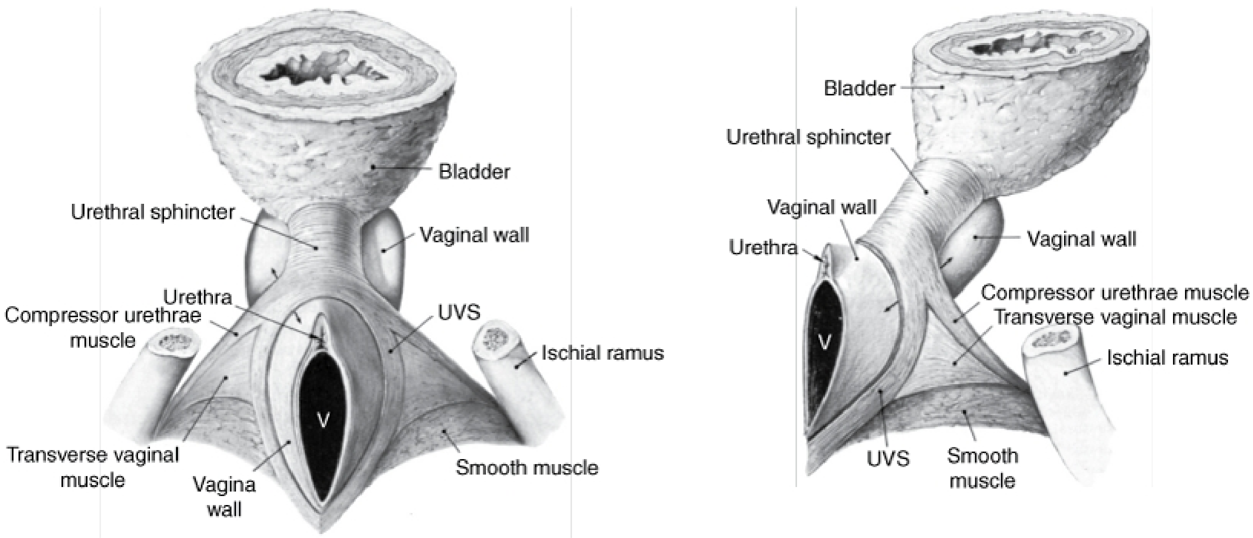
The nerve supply to the bladder arises from the vesical plexus, a component of the inferior hypogastric plexus (Inferior Hypogastric Plexus).

Urethra

The female urethra is a complex organ that is 3 to 4 cm in length. The lumen of the urethra begins at the internal urinary meatus and then courses through the bladder base for less than a centimeter. This region of the bladder where the urethral lumen traverses the bladder base is called the *vesical neck.* The distal two thirds of the urethra are fused with the anterior vaginal wall.

The walls of the urethra begin outside the bladder wall. They consist of two layers of smooth muscle, an inner longitudinal and an outer circular layer. This outer layer, in turn, surrounded by a circular layer of skeletal muscle referred to as the *sphincter urethra* or *rhabdosphincter* (see Fig. 23-5). Approximately at the junction of the middle and lower thirds of the urethra and just above the perineal membrane, two strap skeletal muscles known as the *urethrovaginal sphincter* and *compressor urethrae* are found. These muscles were known previously as the *deep transverse perineal muscles* in females. Combined, the urethrovaginal sphincter, the compressor urethrae, and the sphincter urethra constitute the *striated urogenital sphincter complex* (Fig. 38-20). Together, these three muscles function as a unit and have a complex and controversial innervation, as described below. Their fibers combine to provide constant tonus, with emergency reflex activity mainly in the distal half of the urethra.

FIGURE 38-20



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Striated urogenital sphincter complex in the female. The perineal membrane has been removed. UVS = urethrovaginal sphincter; V = vagina; VW = vaginal wall. *(From Oelrich, 1983, with permission.)*

Distal to the level of the perineal membrane, the walls of the urethra consist of fibrous tissue, serving as the nozzle that directs the urine stream. The urethra has a prominent submucosal layer that is lined by hormone-sensitive stratified squamous epithelium. Within the submucosal layer on the dorsal or vaginal surface of the urethra is a group of glands known as the *paraurethral glands* that open into the lumen of the dorsal surface of the urethra (see Fig. 26-4). Duct openings of the two most prominent glands, termed *Skene glands,* are seen on the inner surface of the external urethral orifice.

Clinical Correlation

Obstruction of the paraurethral gland ducts can result in cyst formation, and chronic infection of the paraurethral glands can lead to urethral diverticula (see Chap. 26, Classification).

The urethra receives its blood supply from branches of the vesical and internal pudendal arteries. The pudendal nerve innervates the most distal part of the striated urogenital sphincter complex. Somatic efferent branches of the pelvic nerve, a component of the inferior hypogastric or pelvic plexus, variably innervate the sphincter urethra.

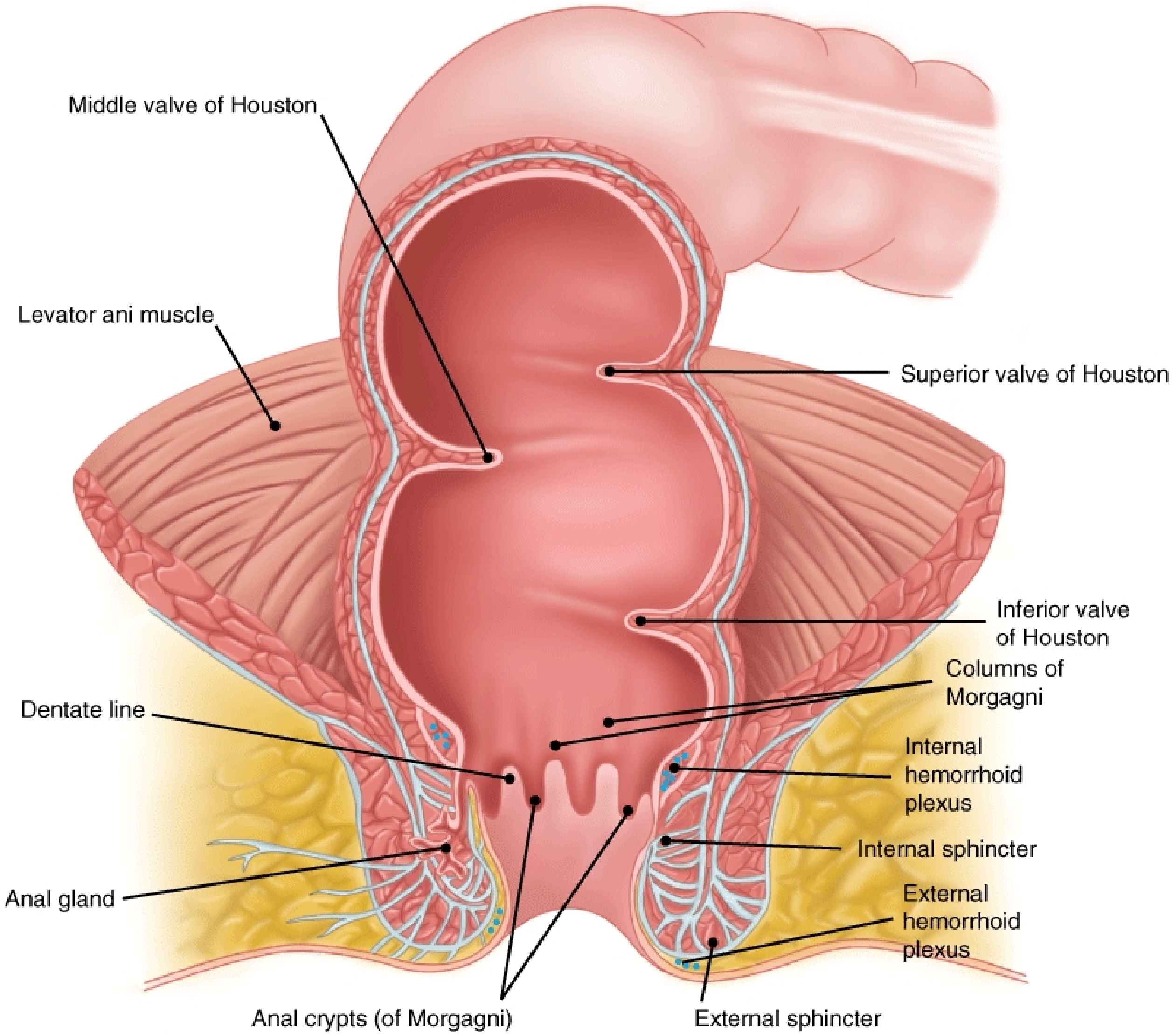
Ureters

A detailed description of the pelvic ureter appears in the discussion of pelvic sidewall anatomy (Pelvic Sidewall).

RECTUM

The rectum is continuous with the sigmoid colon approximately at the level of the third sacral vertebra. It descends on the anterior surface of the sacrum for about 12 cm and ends in the anal canal after passing through the levator hiatus (see Fig. 38-7). The anterior and lateral portions of the proximal two thirds of the rectum are covered by peritoneum. The peritoneum is then reflected onto the posterior vaginal wall, forming the posterior cul-de-sac of Douglas, also termed the *rectouterine pouch* (see Fig 38-14). In females, the cul-de-sac is located approximately 5 to 6 cm from the anal orifice and can be palpated manually during rectal or vaginal examination (see Fig. 1-7). At its commencement, the rectal wall is similar to that of the sigmoid, but near its termination, it becomes dilated to form the rectal ampulla, which begins below the posterior cul-de-sac peritoneum (Fig. 38-21).

FIGURE 38-21



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Rectal anatomy. *(From Pfenninger, 2001, with permission.)*

The rectum contains several (usually three) transverse folds, *plicae transversales recti,* also termed *valves of Houston* . The largest and most constant of these folds is located anteriorly and to the right, approximately 8 cm from the anal orifice. These folds may contribute to fecal continence by supporting fecal matter above the anal canal.

Clinical Correlation

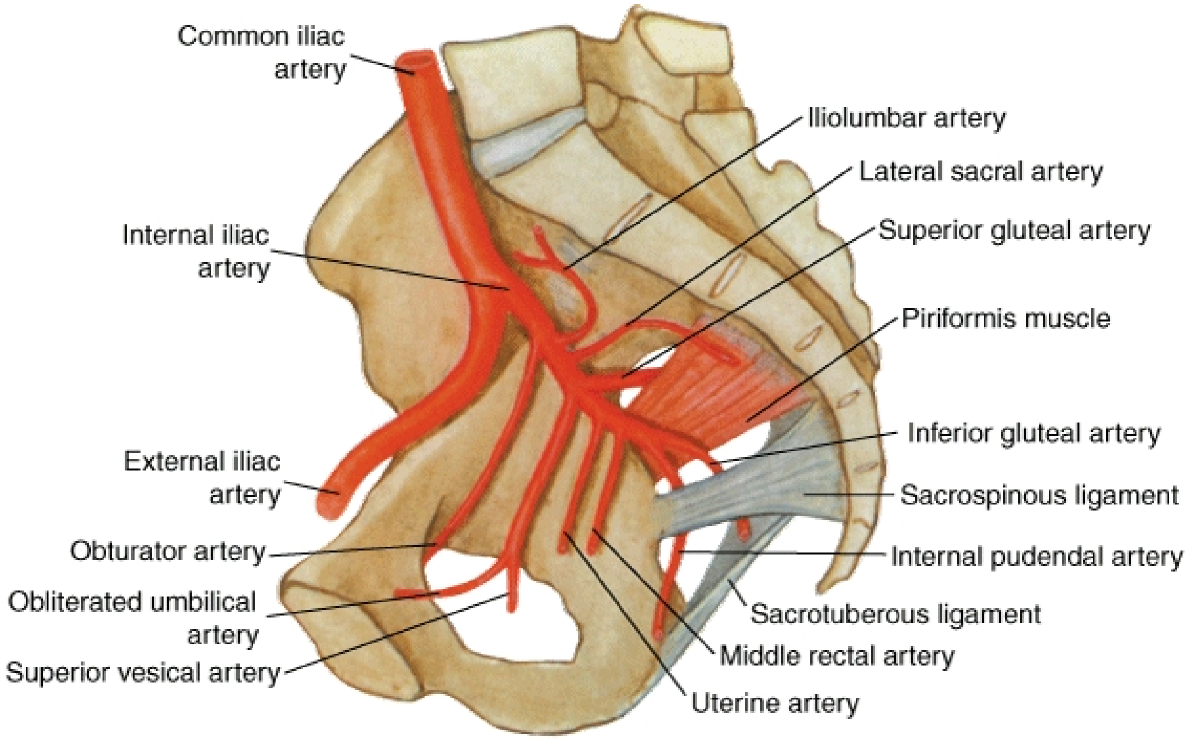
In the empty state, the transverse rectal folds overlap each other, making it difficult at times to manipulate an examining finger or endoscopic tube past this level.

Pelvic Blood Supply

The pelvic organs are supplied by the visceral branches of the internal iliac (hypogastric) artery and by direct branches from the abdominal aorta (Fig. 38-22). The internal iliac artery generally divides into anterior and posterior divisions in the area of the greater sciatic foramen. Each division has three parietal branches that supply nonvisceral structures. The *iliolumbar* , *lateral sacral* , and *superior gluteal arteries* are the three parietal branches of the posterior division. The *inferior gluteal, internal pudendal,* and

obturator arteries are parietal branches that most commonly arise from the anterior division. The remaining branches of the anterior division supply the pelvic viscera (bladder, uterus, vagina, and rectum). These include the *uterine* , *vaginal* , and *middle rectal arteries* and the *superior vesical arteries* , which commonly arise from the patent part of the umbilical arteries.

FIGURE 38-22



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Pelvic arteries. *(From Clemente, 1997, with permission.)*

The two most important branches of the aorta that contribute to the blood supply of the pelvic organs are the *superior rectal* and *ovarian arteries* (see Fig. 38-15). The superior rectal arteryis the terminal branch of the inferior mesenteric artery. The superior rectal arteries anastomoses with the middle rectal arteries, thus contributing blood supply to the rectum and vagina. The ovarian arteries arise directly from the aorta just inferior to the renal vessels. The ovarian arteries anastomose with the ascending branch of the uterine artery. These anastomoses contribute to the blood supply of the uterus and adnexa.

Other important anastomoses between the aorta and internal iliac arteries include those of the middle sacral and lumbar arteries with the lateral sacral and iliolumbar arteries, respectively.

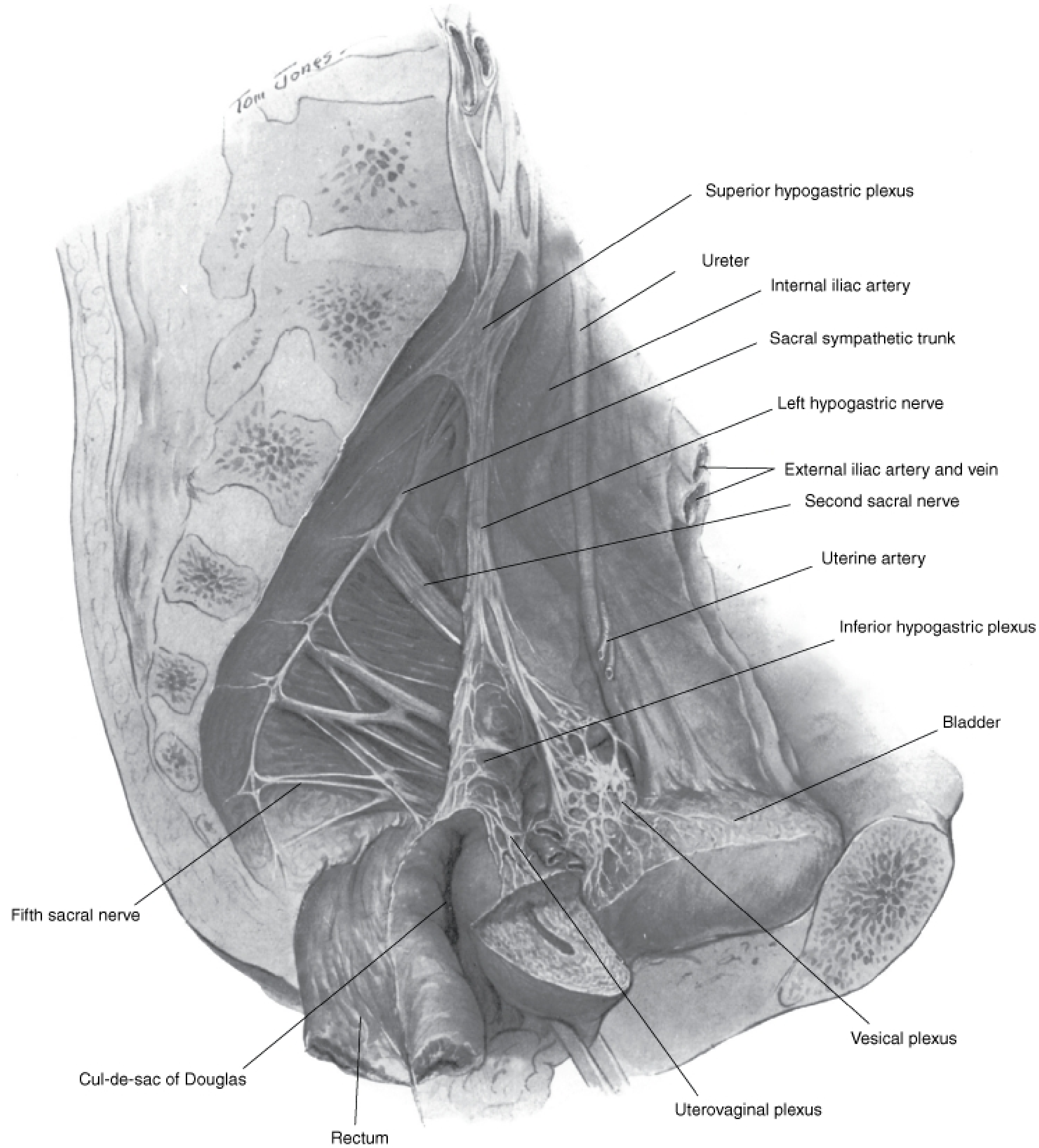
Pelvic Innervation

Nerve supply to the visceral structures in the pelvis (bladder, urethra, vagina, uterus, adnexa, and rectum) arises from the autonomic nervous system. The two most important components of this system in the pelvis include the *superior* and *inferior hypogastric plexuses* .

SUPERIOR HYPOGASTRIC PLEXUS

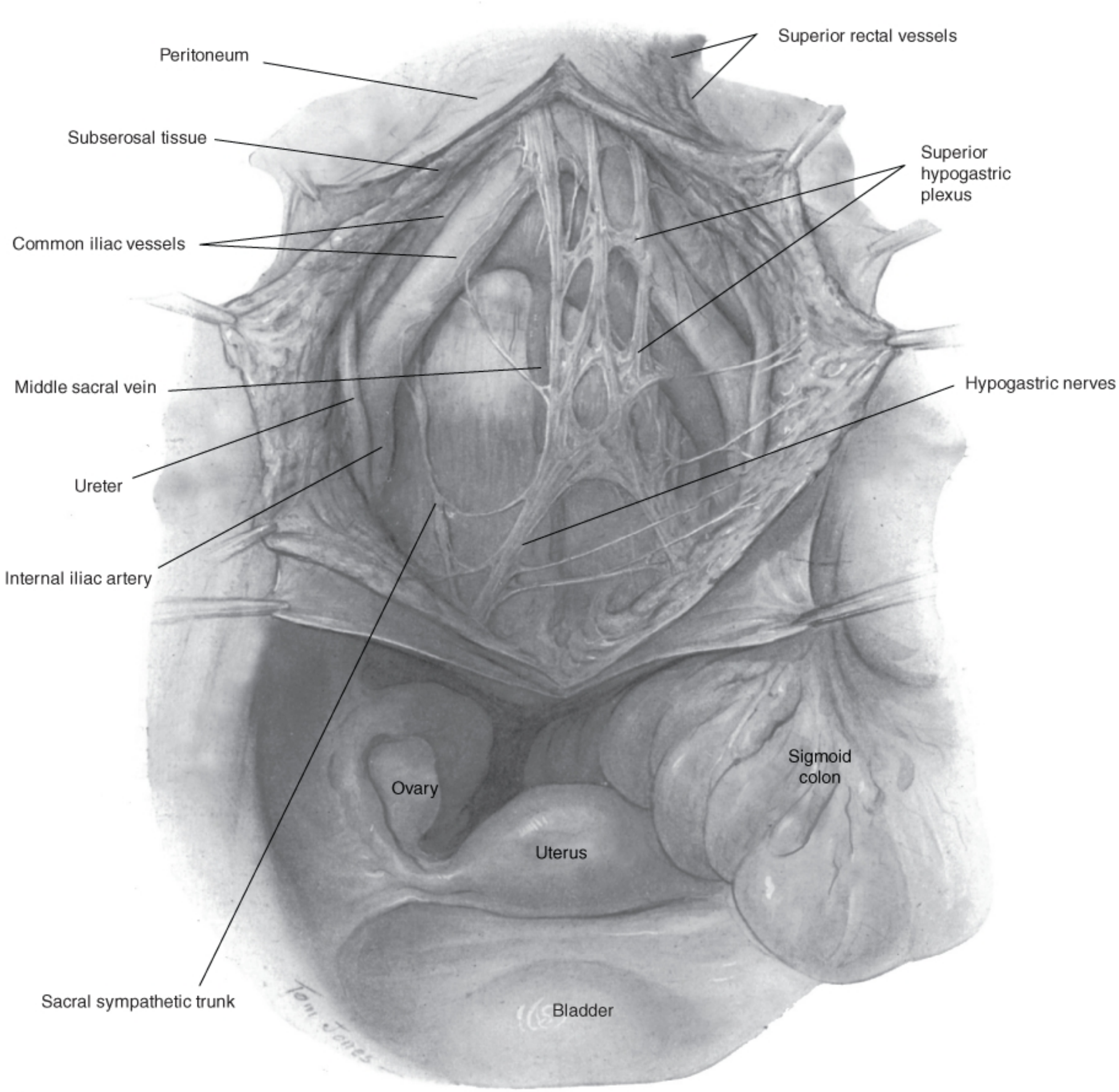
The superior hypogastric plexus, also known as the *presacral nerve,* is an extension of the aortic plexus found below the aortic bifurcation (Fig. 38-23A). This plexus contains primarily sympathetic fibers and sensory afferent fibers from the uterus.

FIGURE 38-23



A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

A. Pelvic innervation **B.** Superior and inferior hypogastric plexuses. *(From Anson, 1950, with permission.)*

The sensory afferent fibers contained within the superior hypogastric plexus are targeted in presacral neurectomy, a surgical procedure performed to treat dysmenorrhea and central pelvic pain refractory to medical management (see Chap. 11, Neurolysis).

INFERIOR HYPOGASTRIC PLEXUS

The superior hypogastric plexus terminates by dividing into the *hypogastric nerves* . These nerves join parasympathetic efferents from the second through the fourth sacral nerve roots (pelvic splachnic nerves, also termed *nervi erigentis*) to form the inferior hypogastric plexus, also known as the *pelvic plexus* (Fig. 38-23B).

Fibers of the inferior hypogastric plexus accompany the branches of the internal iliac artery to the pelvic viscera. Accordingly, they are divided into three portions: the vesical, uterovaginal (Frankenhauser ganglion), and middle rectal plexuses. Extensions of the

inferior hypogastric plexus reach the perineum along the vagina and urethra to innervate the clitoris and vestibular bulbs.

Injury to the branches of the inferior hypogastric plexus during cancer debulking or other extensive pelvic surgeries can lead to varying degrees of voiding, sexual, and defecatory dysfunction.

Retroperitoneal Surgical Spaces

Knowledge of a number of retroperitoneal spaces is important for the pelvic surgeon. These spaces include the pelvic sidewall, the presacral space, and prevesical space.

PELVIC SIDEWALL

The retroperitoneal space of the pelvic walls contains the internal iliac vessels and pelvic lymphatics, pelvic ureter, and obturator nerve. Entering this space is especially useful for identifying the ureter and for ligating the uterine or internal iliac arteries in the setting of hemorrhage.

Vessels

The major pelvic vessels are shown in Figure 38-22. The internal iliac artery and vein are within the pelvic sidewall retroperitoneal space. If these vessels are dissected, such as for internal iliac or uterine artery ligation, the ureter must be avoided. Ligation of the internal iliac artery is usually done to decrease the pulse pressure to pelvic organs. The vessel should be ligated distal to the origin of the posterior division branches in an effort to prevent significant devascularization of the gluteal muscles. These branches generally arise from the lateral wall of the internal iliac artery about 3 to 4 cm from its division off the common iliac artery.

Pelvic Ureter

The ureter enters the pelvis by crossing over the bifurcation of the common iliac artery just medial to the ovarian vessels (see Figs. 38-12 and 38-15). It descends into the pelvis attached to the medial leaf of the pelvic sidewall peritoneum. Along this course, the ureter lies medial to the internal iliac branches and anterolateral to the uterosacral ligaments. The ureter then traverses the cardinal ligament approximately 1 to 2 cm lateral to the cervix. Near the level of the uterine isthmus, it courses below the uterine artery ("water under the bridge") (see Fig. 38-13 and Fig. 38-14). It then travels anteromedially toward the base of the bladder (see Fig. 38-15). In this path, it runs close to the upper third of the anterior vaginal wall. Finally, the ureter enters the bladder and travels obliquely for approximately 1.5 cm before opening at the ureteral orifice (see Fig. 38-19).

The pelvic ureter receives blood supply from the vessels it passes: the common iliac, internal iliac, uterine, and vesical vessels. Vascular anastomoses on the connective tissue sheath enveloping the ureter form a longitudinal network of vessels.

Because of the pelvic ureter's proximity to many structures encountered during gynecologic surgery, emphasis should be placed on its precise intraoperative identification.

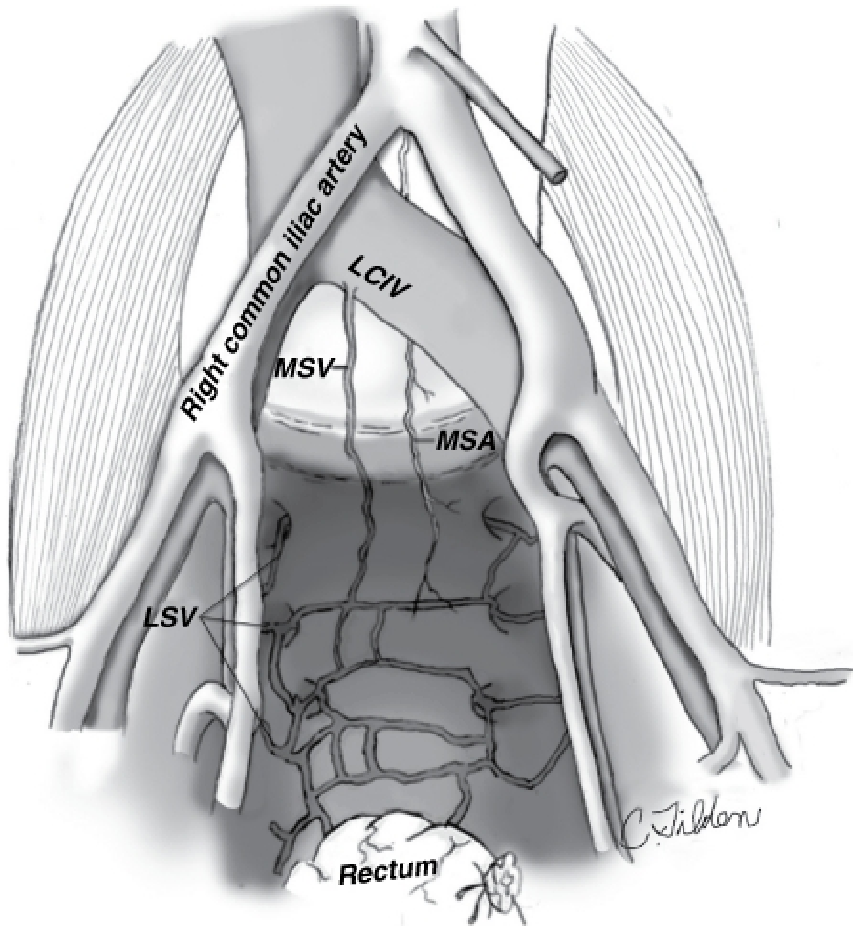
Clinical Correlation

Most ureters are injured during gynecologic surgery for benign disease. Over 50 percent of these injuries are not diagnosed intraoperatively. The most common sites of injury include: (1) the pelvic brim during clamping of the infundibulopelvic ligament, (2) the uterine isthmic region during uterine artery ligation, (3) the pelvic sidewall during suturing of the uterosacral ligament, and (4) the vaginal apex during clamping or suturing of the vaginal cuff.

PRESACRAL SPACE

This retroperitoneal space is located between the sacrum and the rectosigmoid and posterior abdominal wall peritoneum. It begins below the aortic bifurcation and extends inferiorly to the pelvic floor. Laterally, this space is bounded by the internal iliac vessels and branches (Fig. 38-24). Contained within the loose areolar and connective tissue of this space are the superior hypogastric plexus, hypogastric nerves, and portions of the inferior hypogastric plexus (Fig. 38-23).

FIGURE 38-24



Presacral space. LCIV = left common iliac vein; LSV = lateral sacral veins; MSA = middle sacral artery; MSV = middle sacral vein.

The vascular anatomy of the presacral space is complex and includes an extensive and intricate venous plexus, termed the *sacral venous plexus.* This plexus is formed primarily by the anastomoses of the middle and lateral sacral veins on the anterior surface of the sacrum (Fig. 38-24). The middle sacral vein commonly drains into the left common iliac vein, whereas the lateral sacral vein opens into the internal iliac vein. Ultimately, these vessels drain into the caval system. The sacral venous plexus also receives contributions from the lumbar veins of the posterior abdominal wall and from the basivertebral veins that pass through the pelvic sacral foramina.

The middle sacral artery, which courses in proximity to the middle sacral vein, arises from the posterior and distal parts of the abdominal aorta. In a recent study that looked at the vascular anatomy of the presacral space, the left common iliac vein was the closest major vessel identified both cephalad and lateral to the midsacral promontory. The average distance of the left common iliac vein to the midsacral promontory in this study was 2.7 cm (range 0.9 to 5.2 cm) (Wieslander, 2006).

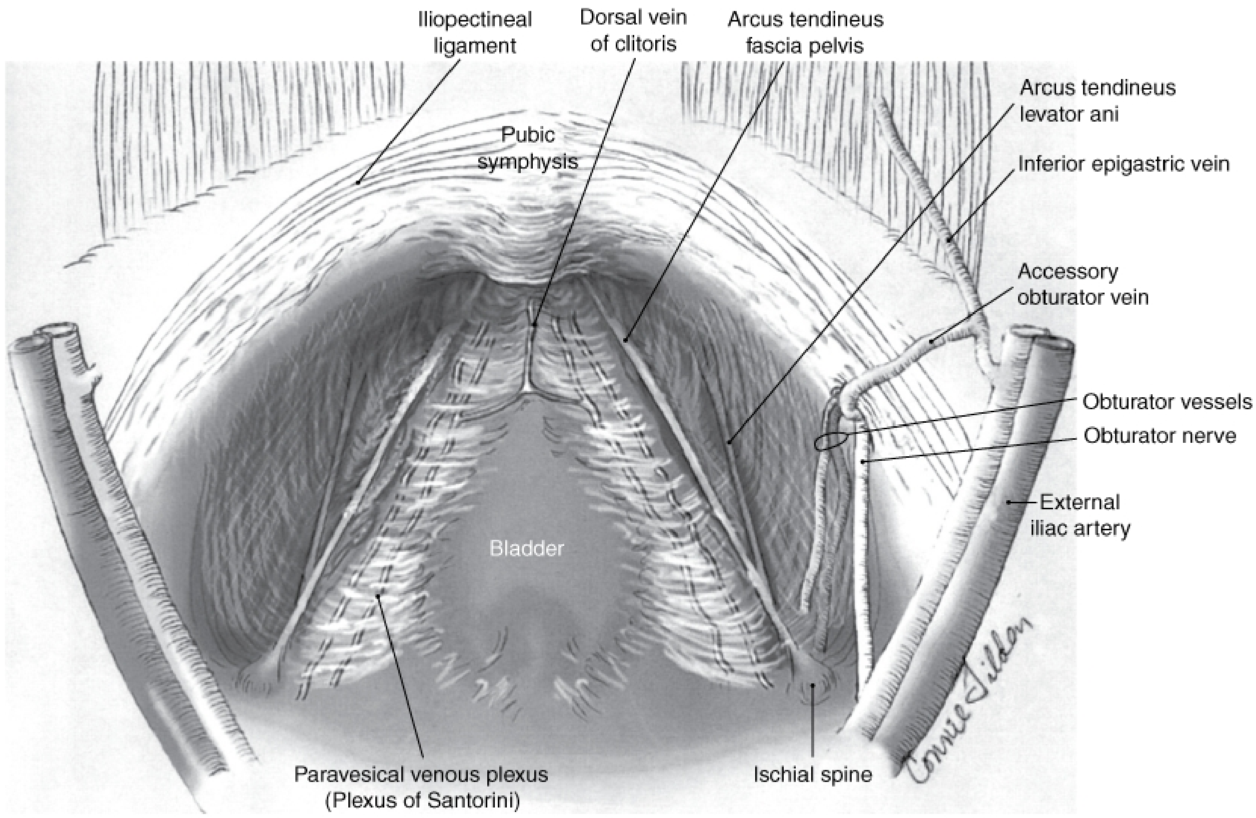
Clinical Correlation

The presacral space is entered by gynecologists to perform abdominal sacrocolpopexy (see Sections 42-17, Abdominal Sacrocolpopexy) and presacral neurectomies. The proximity of the left common iliac vein to the sacral promontory makes this vessel especially vulnerable to injury during entrance into and dissection within this space. Additionally, bleeding from the sacral venous plexus may be difficult to control because the veins often retract into the sacral foramina.

PREVESICAL SPACE

This space is also called the *retropubic space* or *space of Retzius.* It can be entered by incising the transversalis fascial layer of the anterior abdominal wall. As shown in Figure 38-25, this space is bounded anteriorly and laterally by the bony pelvis and muscles of the pelvic wall. This space is closed by the anterior abdominal wall superiorly. The bladder and proximal urethra lie posterior to this space. Attachments of the paravaginal connective tissue to the arcus tendineus fascia pelvis constitute the posterolateral limit of the space and separate it from the vesicovaginal and vesicocervical spaces.

FIGURE 38-25



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Retropubic space.

There are a number of vessels and nerves in this space. The *dorsal vein of the clitoris* passes under the lower border of the pubic symphysis and drains into the periurethral-perivesical venous plexus, also termed the *plexus of Santorini.* The obturator neurovascular bundle courses along the lateral pelvic walls and enters the obturator canal to reach the medial compartment of the thigh. The autonomic nerve branches that supply the bladder and urethra course on the lateral borders of these structures. Additionally, in most women, accessory obturator vessels that arise from the inferior epigastric or external iliac vessels are found crossing the superior pubic rami and connecting with the obturator vessels near the obturator canal.

Clinical Correlation

Injury to the obturator neurovascular bundle or accessory obturator vessels is most often associated with pelvic lymph node dissections and paravaginal defect repair procedures. Thus, knowledge of the approximate location of these vessels and of the obturator canal is critical when this space is dissected. The obturator canal is found approximately 5 to 6 cm from the midline of the pubic symphysis and 1 to 2 cm below the upper margin of the iliopectineal ligament (Drewes, 2005).

Bleeding from the periurethral-perivesical venous plexus is often encountered while placing the sutures or passing the needles into

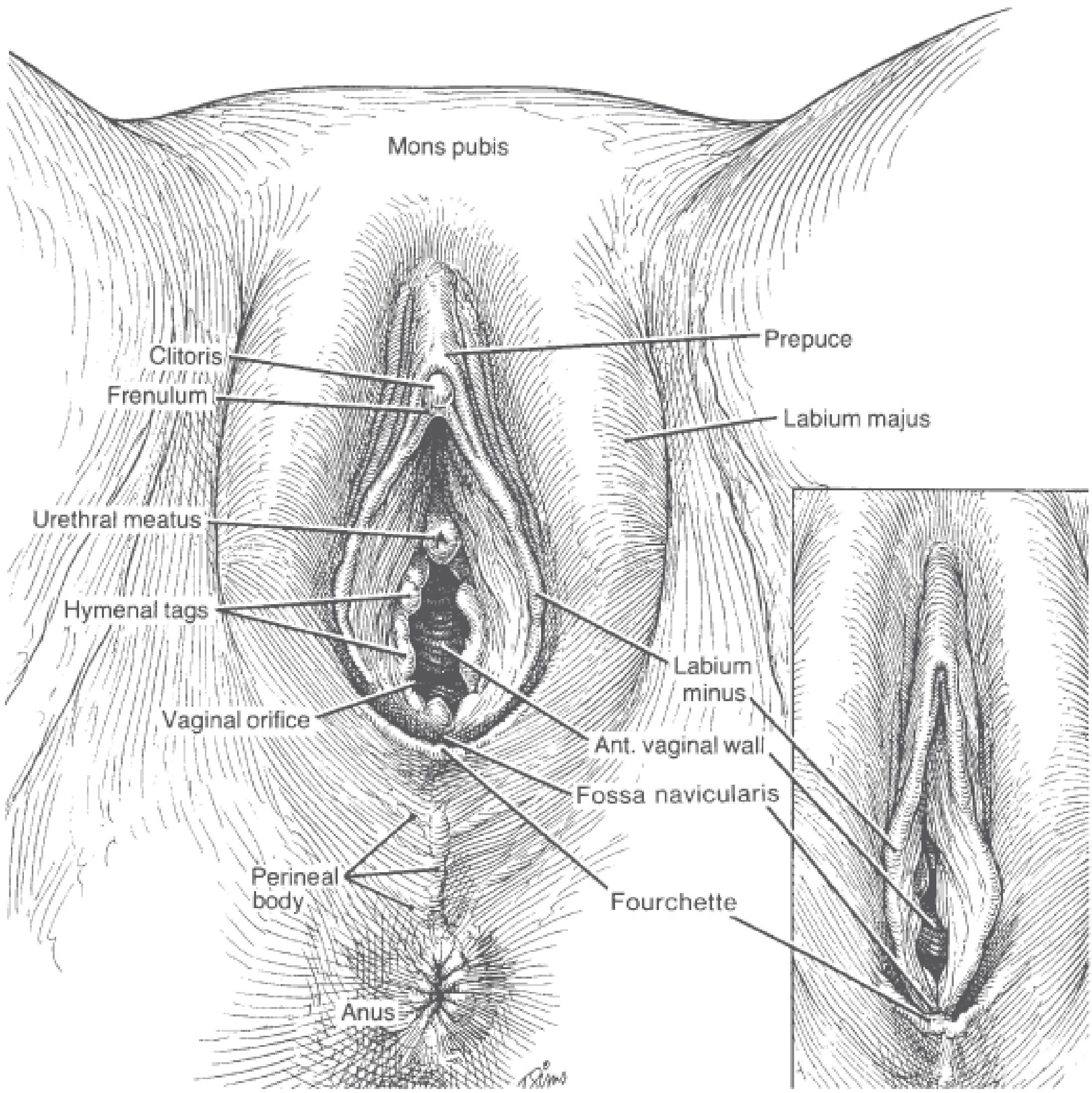
this space during retropubic bladder neck suspensions and midurethral retropubic procedures, respectively. This venous ooze usually stops when pressure is applied or the sutures are tied.

VULVA AND PERINEUM

Vulva

The external female genitalia, collectively known as the *vulva,* lie on the pubic bones and extends posteriorly under the pubic arch. Structures included are the mons pubis, labia majora, labia minora, clitoris, vestibule, vestibular bulbs, greater vestibular (Bartholin) glands, lesser vestibular glands, paraurethral (Skene) glands, and the urethral and vaginal orifices (Fig. 38-26). The embryologic development of these structures can be found in Chapter 18.

FIGURE 38-26



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

External female genitalia. *(From Cunningham, 2005, with permission.)*

MONS PUBIS AND LABIA MAJORA

The *mons pubis* , also called the *mons veneris* , is the rounded eminence that lies anterior to the pubic symphysis. The *labia majora* are two prominent folds that extend from the mons pubis anteriorly toward the perineal body posteriorly. Skin over the mons pubis and labia majora contains hair and has a subcutaneous layer similar to that of the anterior abdominal wall. The subcutaneous layer consists of a superficial fatty layer similar to Camper fascia and a deeper membranous layer, called *Colles fascia.* Also known as the *superficial perineal fascia,* Colles fascia is similar and continuous with Scarpa fascia of the anterior abdominal wall (see Fig. 38-4).

Clinical Correlation

Colles fascia attaches firmly to the ischiopubic rami laterally and the perineal membrane posteriorly. These attachments prevent the spread of fluid, blood, or infection from the superficial perineal space to the thighs or posterior perineal triangle. Anteriorly, Colles fascia has no attachments to the pubic rami, and it is therefore continuous with the lower anterior abdominal wall. This continuity may allow the spread of fluid, blood, and infection between these compartments.

The round ligament and obliterated processus vaginalis, also termed the *canal of Nuck,* exit the inguinal canal and attach to the adipose tissue or skin of the labia majora (see Fig. 38-4). Thus, the differential diagnosis of a mass in the labium majus should include a leiomyoma arising from the round ligament or a persistent processus vaginalis. A congenital inguinal hernia also may reach the labium majus.

LABIA MINORA

These two cutaneous folds lie between the labia majora (Fig. 38-26). Anteriorly, each labium minus bifurcates to form two folds that surround the glans of the clitoris. The *prepuce* is the anterior fold that overlies the glans, and the *frenulum* is the fold that passes below the clitoris. Posteriorly, the labia minora end at the fourchette.

In contrast to the skin that overlies the labia majora, the skin of the labia minora does not contain hair. Also, the subcutaneous tissue is devoid of fat and consists primarily of loose connective tissue. This latter attribute allows mobility of the skin during intercourse and accounts for the ease of dissection with vulvectomy.

Clinical Correlation

Typically, labia minora are symmetric, but their size and shape can vary widely between women. In some, these winglike structures are pendulous and can be drawn into the vagina during coitus. If associated with dyspareunia in this setting, the labia can be reduced surgically (see Section 41-10, Labial Minora Reduction). Moreover, chronic dermatologic diseases such as lichen sclerosus may lead to significant atrophy or disappearance of the labia minora (see Chap. 4, Lichen Sclerosus).

CLITORIS

This is the female erectile structure homologous to the penis. It consists of a glans, a body, and two crura. The glans contains many nerve endings and is covered by a mucous membrane. The body measures approximately 2 cm and is connected to the pubic ramus by the crura.

VAGINAL VESTIBULE

This is the area between the two labia minora. It is bounded laterally by the line of Hart and medially by the hymenal ring. The Hart line demarcates changes in epithelium. Beyond Hart line the stratified squamous epithelium has a thin keratin layer. Inside Hart line, the epithelium is nonkeratinized. The vestibule extends from the clitoris anteriorly to the fourchette posteriorly (see Fig. 38-26). It contains the openings of the urethra, vagina, greater vestibular glands (also known as *Bartholin glands*), and Skene glands, which are the largest pair of paraurethral glands. It also contains the numerous openings of the lesser vestibular glands. A shallow vestibular depression known as the *navicular fossa* lies between the vaginal orifice and the fourchette.

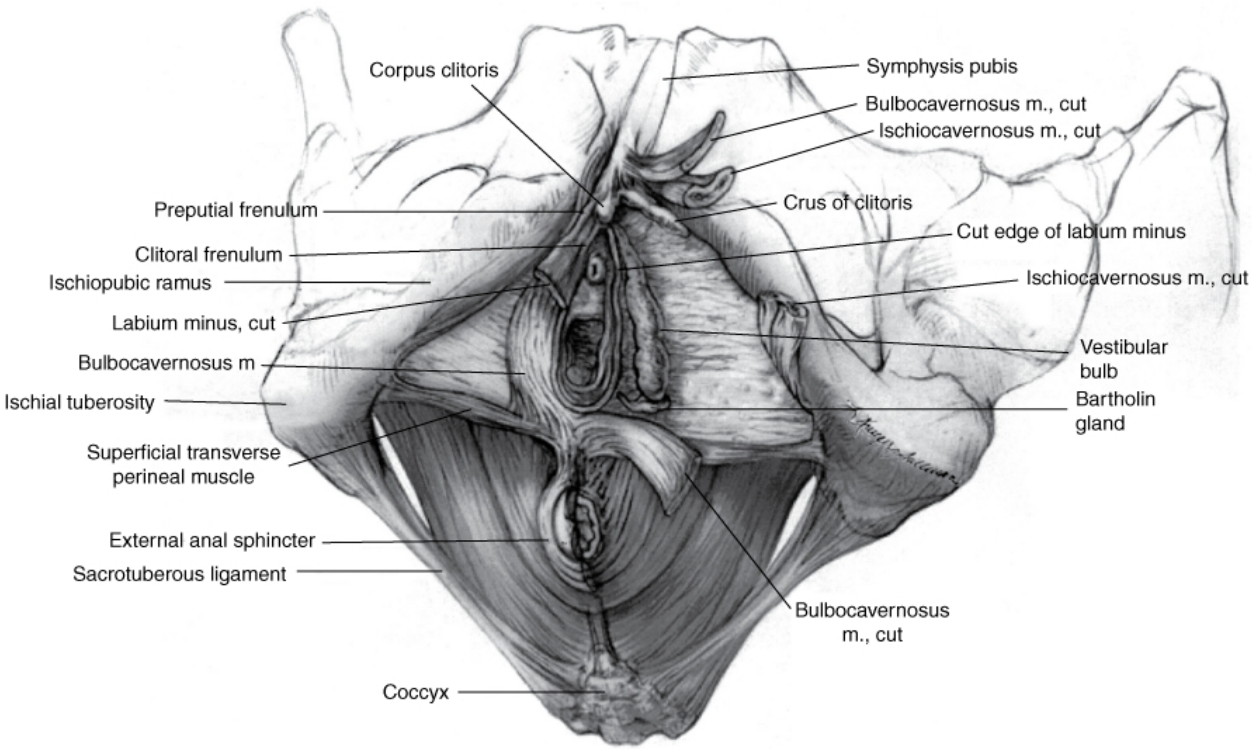
CLINICAL CORRELATION

The Hart line is clinically relevant when choosing incision sites for Bartholin gland duct drainage or marsupialization (see Section 41-6, Bartholin Gland Duct Incision and Drainage). In attempts to recreate near-normal gland duct anatomy following these procedures, incisions placed external to Hart line should be avoided (Kaufman, 1994).

VESTIBULAR BULBS

These are homologues to the male penile bulb and corpus spongiosum. They are two elongate, approximately 3-cm-long, richly vascular erectile masses that surround the vaginal orifice (Fig. 38-27). Their posterior ends are in contact with the Bartholin glands. Their anterior ends are joined to one another and to the clitoris. Their deep surfaces are in contact with the perineal membrane, and their superficial surfaces are partially covered by the bulbocavernosus muscles.

FIGURE 38-27



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Perineal structures and superficial perineal space.

Clinical Correlation

The proximity of the Bartholin glands to the vestibular bulbs accounts for the significant bleeding sometimes encountered with Bartholin gland excision (see Section 41-8, Bartholinectomy).

GREATER VESTIBULAR OR BARTHOLIN GLANDS

Also known as Bartholin glands, these are the homologues of the male bulbourethral or Cowper glands. They are in contact with and often overlapped by the posterior ends of the vestibular bulbs (see Fig. 38-27). Each gland is connected to the vestibule by an approximately 2-cm-long duct. The ducts open in the groove between the labia minora and the hymenâ€"the vestibuleâ€"at approximately 5 and 7 o'clock positions.

The glands contain columnar cells that secrete clear or whitish mucus with lubricant properties. These glands are stimulated by sexual arousal. Contraction of the bulbocavernosus muscle, which covers the superficial surface of the gland, stimulates gland secretion.

Clinical Correlation

Obstruction of the Bartholin ducts by proteinaceous material or by inflammation from infection can lead to cysts of variable sizes. An infected cyst can lead to an abscess that is drained surgically. Symptomatic or recurrent cysts may require marsupialization or gland excision (see Sections 41-7, Marsupialization and 41-8, Bartholinectomy).

Perineum

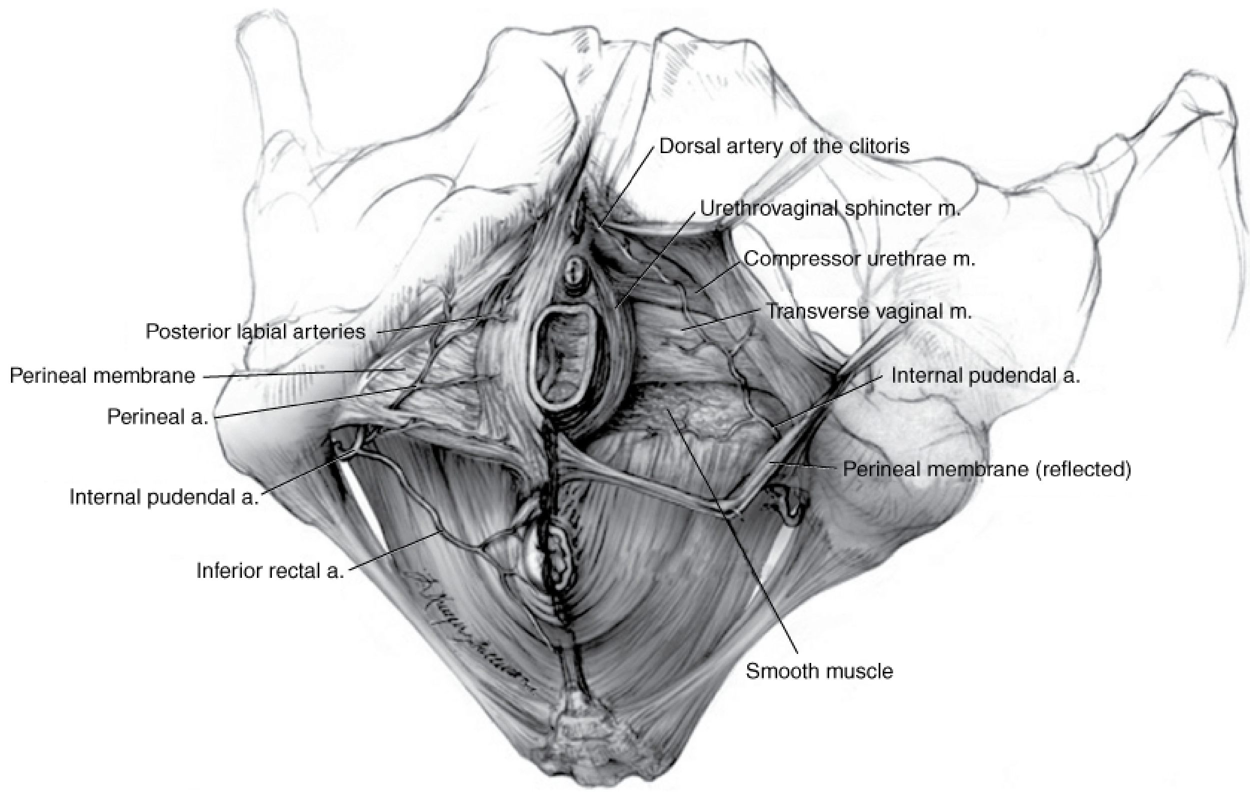
The *perineum* is the diamond-shaped area between the thighs (see Fig. 38-26). It is bounded deeply by the inferior fascia of the pelvic diaphragm and superficially by the skin between the thighs. The anterior, posterior, and lateral boundaries of the perineum are the same as those of the bony pelvic outlet: the pubic symphysis anteriorly, ischiopubic rami and ischial tuberosities anterolaterally, coccyx posteriorly, and sacrotuberous ligaments posterolaterally (see Fig. 38-27). An arbitrary line joining the ischial tuberosities divides the perineum into the anterior or urogenital triangle and a posterior or anal triangle.

ANTERIOR (UROGENITAL) TRIANGLE

As discussed earlier, structures that comprise the vulva or external female genitalia lie in the anterior triangle of the perineum. The base or posterior border of this triangle is the interischial line that usually overlies the superficial transverse perineal muscles (see Fig. 38-27).

The anterior triangle can be further divided into a superficial and a deep pouch or space by the perineal membrane (Fig. 38-28). The superficial perineal space lies below or inferior to the perineal membrane, and the deep space lies above or superior to the membrane.

FIGURE 38-28



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Perineal structures found deep to perineal membrane. Not shown is the inferior rectal nerve, which follows the same course as the inferior rectal artery.

Superficial Perineal Space

This space of the anterior triangle is an enclosed compartment that lies between Colles fascia and the perineal membrane. It contains the ischiocavernosus, bulbocavernosus, and superficial transverse perineal muscles; Bartholin glands; vestibular bulbs; clitoris; and branches of the pudendal vessels and nerve (see Figs. 38-8 and 38-27). The urethra and vagina traverse this space.

The *ischiocavernosus muscle* attaches to the medial aspect of the ischial tuberosities posteriorly and the ischiopubic rami laterally. Anteriorly, it attaches to the crus of the clitoris. This muscle may help to maintain clitoral erection by compressing the crus of the clitoris, thus retarding venous drainage.

The *bulbocavernosus muscle* , also termed the *bulbospongiosus muscle,* covers the superficial portion of the vestibular bulbs and Bartholin glands. These muscles attach to the body of the clitoris anteriorly and the perineal body posteriorly. The muscles act to constrict the vaginal lumen, contributing to the release of secretions from Bartholin glands. They also may contribute to clitoral erection by compressing the deep dorsal vein of the clitoris. The bulbocavernosus muscle, along with the ischiocavernosus muscle, acts to pull the clitoris downward.

The *superficial transverse perineal muscles* are narrow strips that attach to the ischial tuberosity laterally and the perineal body medially. They may be attenuated or even absent, but when present, they contribute to the perineal body.

Deep Perineal Space

This pouch lies deep or superior to the perineal membrane (see Fig. 38-28). In contrast to the superficial perineal space, which is a closed compartment, the deep space is continuous superiorly with the pelvic cavity. It contains the compressor urethrae and urethrovaginal sphincter muscles, external urethral sphincter, parts of urethra and vagina, branches of the internal pudendal artery, and the dorsal nerve and vein of the clitoris.

Perineal Membrane

Traditionally, a trilaminar, triangular urogenital diaphragm has been described as the main component of the deep perineal pouch. According to this concept, the urogenital diaphragm consisted of the deep transverse perineal muscles and sphincter urethrae muscles between the perineal membrane (inferior fascia of the urogenital diaphragm) and a superior layer of fascia (superior fascia of the urogenital diaphragm). However, the term *diaphragm* is used to describe a closed compartment. As described earlier, the deep pouch is an open compartment. It is bounded inferiorly by the perineal membrane and extends up into the pelvis (Oelrich, 1980, 1983). As a result, when describing perineal anatomy, the terms *urogenital diaphragm* and *inferior fascia of the urogenital diaphragm* are misnomers and have been replaced by the anatomically correct term *perineal membrane.*

The perineal membrane is a sheet of dense fibrous tissue that spans the opening of the anterior pelvic outlet (see Figs. 38-8 and 38-28). It constitutes the superior boundary of the superficial perineal space, as described earlier. The perineal membrane attaches laterally to the ischiopubic rami, medially to the distal third of the urethra and vagina, and posteriorly to the perineal body. Anteriorly, it attaches to the arcuate ligament of the pubis. In this area the perineal membrane is particularly thick and is referred to as the *pubourethral ligaments.*

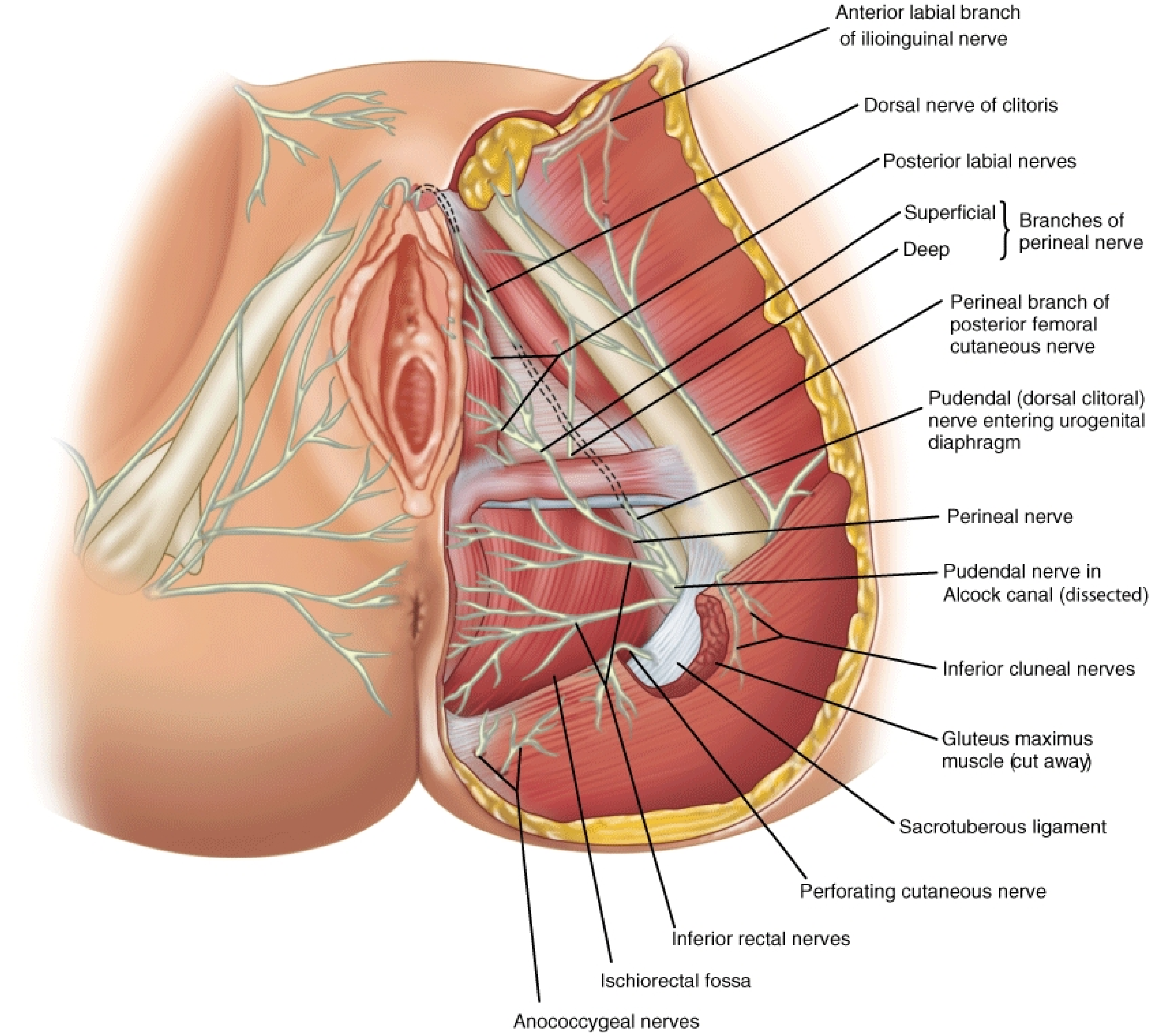
Clinical Correlation

The perineal membrane attaches to the lateral walls of the vagina approximately at level of the hymen. It provides support to the distal vagina and urethra by attaching these structures to the bony pelvis.

POSTERIOR (ANAL) TRIANGLE

This triangle contains the ischioanal fossa, anal canal, anal sphincter complex and branches of the internal pudendal vessels and pudendal nerve. It is bounded deeply by the fascia overlying the inferior surface of the levator ani muscles and laterally by the fascia overlying the medial surface of the obturator internus muscles. A splitting of the obturator internus fascia in this area is known as the *pudendal* or *Alcock canal* (see Fig. 38-30). This canal allows passage of the internal pudendal vessels and pudendal nerve before these structures split into terminal branches to supply the structures of the vulva and perineum.

FIGURE 38-30



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Nerves of the perineum and external genitalia. *(From Netter, 1989, with permission.)*

Ischiorectal Fossa

The ischioanal or ischiorectal fossa fills the majority of the anal triangle (see Fig. 38-30). It contains adipose tissue and occasional blood vessels. The anal canal and anal sphincter complex lie in the center of this fossa. The ischioanal fossa is bounded superomedially by the inferior fascia of the levator muscles, anterolaterally by the fascia covering the medial surface of the obturator internus muscles and the ischial tuberosities, and posterolaterally by the lower border of the gluteus maximus muscles and sacrotuberous ligaments. At a superficial level, the ischioanal fossa is bounded anteriorly by the superficial transverse perineal muscles. At a superior or deeper level, there is no fascial boundary between the fossa and the tissues deep to the perineal membrane. Posterior to the anus, the contents of the fossa are continuous across the midline except for the attachments of the external anal sphincter fibers to the coccyx. The continuity of the ischioanal fossa across perineal compartments allows fluid, infection, and malignancy to spread from one side of the anal canal to the other, as well as into the perineal compartment deep to

the perineal membrane.

Anal Sphincter Complex

This complex consists of two sphincters and the puborectalis muscle.

External Anal Sphincter

This consists of striated muscle that surrounds the distal anal canal. It consists of a superficial and a deep portion (see Fig. 38-21). The more superficial fibers lie below the internal sphincter and are separated from the anal epithelium only by submucosa. The deep fibers blend with the lowest fibers of the puborectalis muscle. The external sphincter is innervated primarily by the inferior anal branch of the pudendal nerve. The external anal sphincter is responsible for the squeeze pressure of the anal canal (see Chap. 25, Anal Sphincter Complex).

Internal Anal Sphincter

This is the thickening of the circular smooth muscle layer of the anal wall. It is under the control of the autonomic nervous system and is responsible for approximately 80 percent of the resting pressure of the anal canal.

Puborectalis Muscle

This comprises the medial portion of the levator ani muscle that arises on either side from the inner surface of the pubic bones. It passes behind the rectum and forms a sling behind the anorectal junction, contributing to the anorectal angle and possibly to fecal continence (see Figs. 38-9 and 38-21).

PERINEAL BODY

This is a mass of fibromuscular tissue found between the distal part of the posterior vaginal wall and the anus. It is formed by the attachment of several structures. Inferiorly or superficially, the structures that attach to and contribute to the perineal body include the bulbocavernosus, superficial transverse perineal, and external anal sphincter muscles (see Fig. 38-27). Structures that attach at a superior or deeper level are the perineal membrane, levator ani muscles and covering fascia, urethrovaginal sphincter muscles, and distal part of the posterior vaginal wall (see Fig. 38-28). The anterior-to-posterior as well as the superior-to-inferior extents of the perineal body measure approximately 2 to 4 cm.

Clinical Correlation

During episiotomy and other vaginal laceration repairs and with pelvic reconstructive procedures, particular attention should be paid to reconstruction of the perineal body in an effort to prevent pelvic organ prolapse and other pelvic floor dysfunction.

Blood Supply, Lymphatics, and Innervation

The vulva and perineum and their contained structures have an intricate of blood, lymphatic, and nerve supply. Within these patterns, a number of anatomic variants are found.

BLOOD VESSELS

The *external pudendal artery* is a branch of the femoral artery and supplies the skin and subcutaneous tissue of the mons pubis (see Figs. 38-3 and 38-4). The *internal pudendal artery* is one of the terminal branches of the internal iliac artery (see Fig. 38-28). It has a long course from its origin, and the association of this vessel with other structures has clinical importance. It exits the pelvis through the greater sciatic foramen, passes behind the ischial spines, and reenters the perineum through the lesser sciatic foramen. It then has a variable course, usually 2 to 3 cm, through the pudendal or Alcock canal and then divides into terminal branches. These are the *inferior rectal* , *perineal* , and *clitoral arteries* . Branches to the perineum sometimes arise from the pudendal artery before it exits the pelvisâ€”these vessels are called *accessory pudendal arteries.* Other accessory vessels also may arise directly from the anterior or posterior division of the internal iliac artery.

The veins that drain the structures of the vulva and perineum have similar courses and names as the arteries. Venous blood from the vestibular bulbs and other structures, with the exception of the erectile tissue of the clitoris, drains into the internal pudendal veins. The erectile tissue drains into the dorsal vein of the clitoris (see Fig. 38-25). This vein courses backwards into the pelvis and

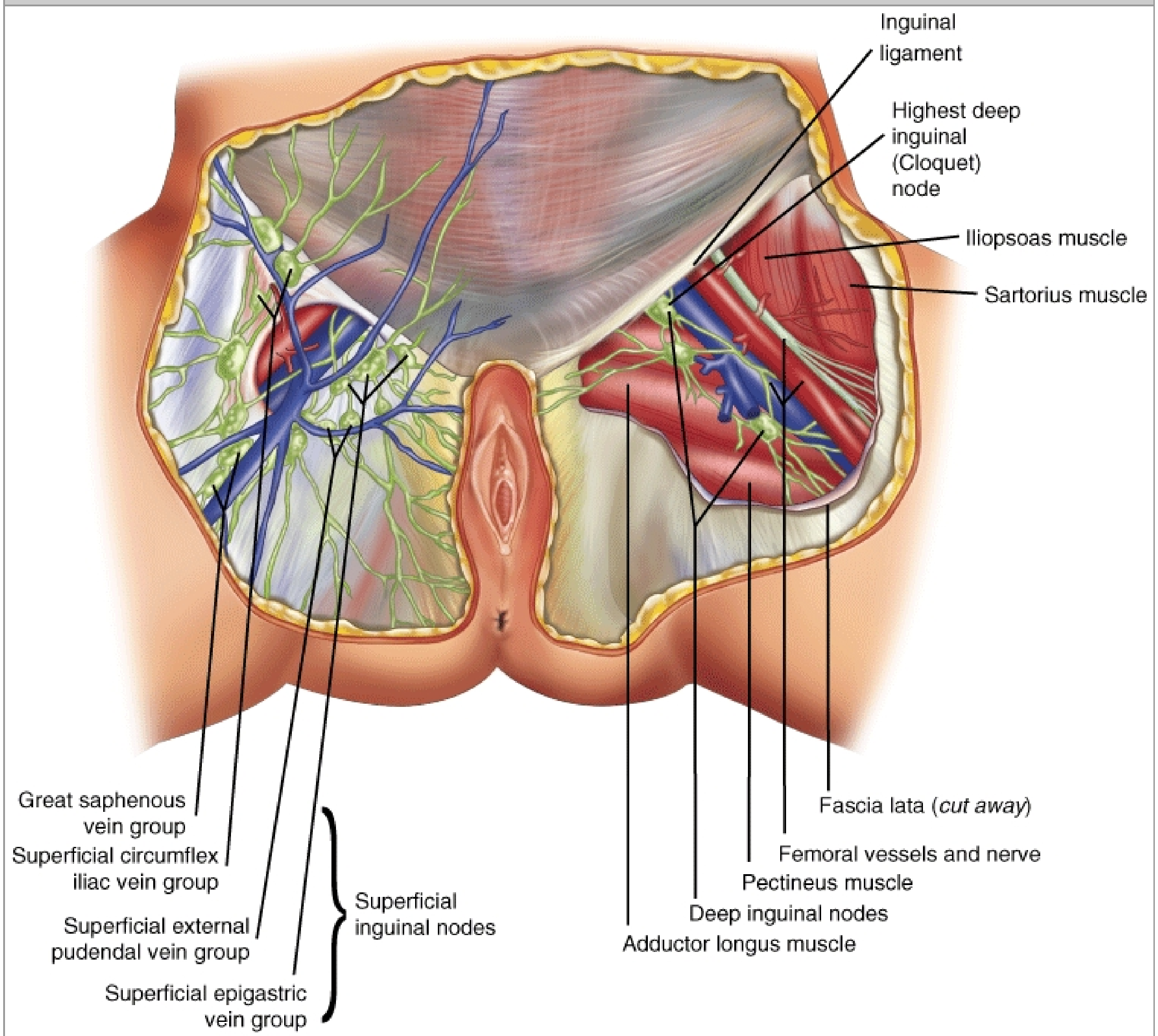
terminates in the periurethral-perivesical venous plexus.

The venous plexus that drains the rectum and anal canal empties into the superior, middle, and inferior rectal veins. The *superior rectal vein* drains into the inferior mesenteric vein, a tributary of the portal vein. The *middle rectal vein* drains into the internal iliac vein. The *inferior rectal vein* drains into the internal pudendal vein and then the internal iliac vein.

LYMPHATIC DRAINAGE

Structures of the vulva and perineum drain into the inguinal lymph nodes, which are located below the inguinal ligament in the upper anterior and medial thigh (Fig. 38-29). There are 10 to 20 inguinal nodes that are divided into a superficial and a deep group. *Superficial inguinal lymph nodes* are more numerous. They are found in the membranous layer of the subcutaneous tissue of the anterior thigh, just superficial to the fascia lata.

FIGURE 38-29



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Superficial inguinal lymph nodes and contents of the femoral triangle. *(From Netter, 1989, with permission.)*

The *deep inguinal nodes* vary from one to three in number and are located deep to the fascia lata in the *femoral triangle* . This triangle is bordered superiorly by the inguinal ligament, laterally by the medial border of the sartorius muscle, and medially by the medial border of the adductor longus muscle. The iliopsoas and pectineus muscles form its floor. Within this triangle, the deep nodes are in the *femoral canal* â€"the space that lies on the medial side of the femoral vein. This canal can communicate with the abdominal cavity through the *femoral ring* . Within the femoral triangle, lateral to medial, the structures found in this space are the femoral nerve, artery, vein, and deep inguinal lymphatics in the femoral canal.

The *fossa ovalis* , or saphenous opening, is an opening in the fascia lata and allows communication of superficial with deep inguinal nodes. When there are three deep inguinal nodes, the highest oneâ€"the Cloquet nodeâ€"is located in the lateral part of the femoral ring. From the deep inguinal nodes, efferent channels pass through the femoral canal and femoral ring to the external iliac nodes (see Fig. 33-2). Lymphatics from the skin of the labia, clitoris, and remainder of the perineum drain into the superficial inguinal nodes. The glans and corpora cavernosa of the clitoris may drain directly to the deep inguinal nodes.

INNERVATION

Somatic Innervation

Branches of the pudendal nerveâ€"inferior anal, perineal, and dorsal nerve of the clitorisâ€"provide sensory and motor innervation to the perineum (Fig. 38-30). The *pudendal nerve* is a branch of the sacral plexus and is formed by the anterior rami of the second through the fourth sacral nerve roots. It has a course and distribution similar to the internal pudendal artery.

Visceral Innervation

Clitoral erection requires parasympathetic visceral efferents derived from the pelvic plexus nerves or nervi erigentes. These arise from the second to the fourth sacral spinal cord segments. They reach the perineum along the urethra and vagina, passing through the urogenital hiatus. Sympathetic fibers reach the perineum with the pudendal nerve.

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PERIOPERATIVE CONSIDERATIONS: INTRODUCTION

Each year, over 30 million surgical procedures are performed. During these, nearly 1 million patients suffer a postoperative complication (Mangano, 2004). As surgeons, gynecologists assume responsibility for assessing a patient's clinical status to identify modifiable risk factors and prevent perioperative morbidity. However, clinicians also should be prepared to diagnose and manage such complications if they arise.

PREOPERATIVE PATIENT EVALUATION

A properly performed preoperative evaluation serves two important functions. It uncovers comorbidities that require further evaluation and optimization to avert perioperative complications. Second, evaluation allows improved use of operating room resources through increased efficiency (Correll, 2006; Roizen, 2000).

Medical Consultation

Often, a thorough preoperative history and physical examination will reveal poorly controlled or previously undiagnosed disease that would benefit from consultation by an internist. The purpose of a preoperative internal medicine consultation is not to obtain "medical clearance", but rather to provide a risk assessment of a woman's current medical state. During consultation, a summary of the surgical illness should be provided, and clear questions are posed to the consultant (Eagle, 2002; Goldman, 1983). In addition, a complete history and physical examination and prior medical records that report previously performed diagnostic testing should be available to the consulting physician. This usually will prevent unnecessary surgical delays due to redundant testing.

Pulmonary Evaluation

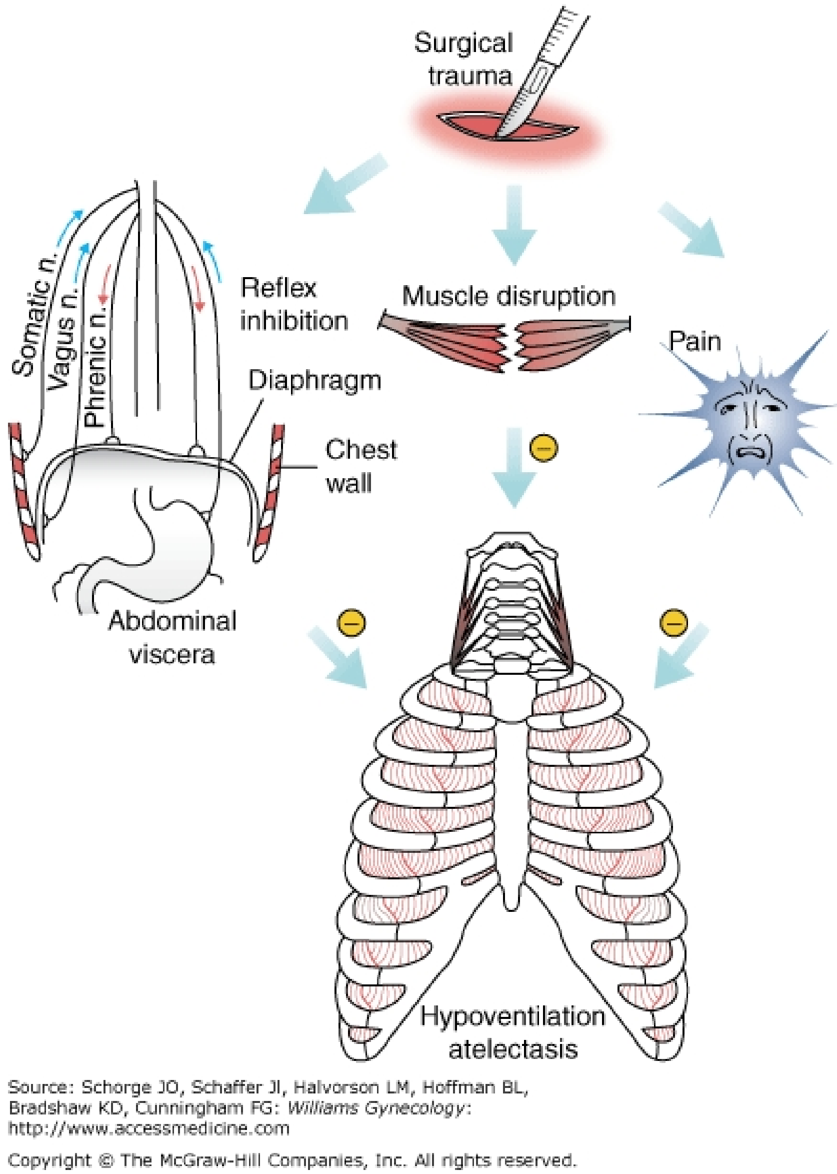
Most postoperative pulmonary morbidity includes atelectasis, pneumonia, and exacerbation of chronic lung diseases.

RISK FACTORS FOR PULMONARY COMPLICATIONS

Procedure-Related Factors

Risk factors for pulmonary complications fall into one of two major categoriesâ€"procedure-related and patient-related. Of these, procedure-related risk factors remain the most important predictors of postoperative complications (Smetana, 1999). For example, upper abdominal incisions as they approach the diaphragm can alter pulmonary function through three mechanisms, as shown in Figure 39-1. As a result, poor diaphragmatic descent postoperatively may result from neurologic, functional, or voluntary disruption during surgery. Poor function may produce persistent decreases in vital capacity and in functional residual capacity and thus predispose patients to atelectasis (Warner, 2000). Surgery duration is another procedure-associated factor. Procedures in which patients receive general anesthesia for longer than 3 hours nearly double the risk of developing a postoperative pulmonary complication. Finally, emergency surgery remains a significant independent predictor of postoperative pulmonary complications. Although these procedure-related risk factors are largely unmodifiable, an appreciation of their associated sequelae should prompt increased postoperative vigilance.

FIGURE 39-1



Surgical factors producing respiratory muscle dysfunction. First, surgical trauma stimulates central nervous system reflexes mediated by both visceral and somatic nerves. These reflexes can inhibit the phrenic nerve. Secondly, muscle disruption impairs respiratory muscle action. Lastly, pain can limit use of respiratory muscles. These factors can reduce lung volumes and produce hypoventilation and atelectasis.

Age

Individuals older than 60 years are at increased risk for developing postoperative pulmonary complications. After stratifying patients for comorbidities, those between 60 and 69 years have a twofold increased, risk. In those older than 70 years, risk is increased threefold (Qaseem, 2006). Baseline cognition should be documented and postoperative sensorium should be monitored because changes may be an early indicator of pulmonary function compromise following surgery.

Smoking

A greater than 20-pack-year smoking history confers a high incidence of postoperative pulmonary complications. Fortunately, this risk can be reduced with smoking abstinence before surgery. Specifically, in preparation for elective surgery, smoking cessation for at least 4 to 8 weeks offers risk reduction (Warner, 1984). Short-term benefits may be related to reduced nicotine and

carboxyhemoglobin levels, improved mucociliary function, decreased upper airway hypersensitivity, and improved wound healing (Moller, 2002; Nakagawa, 2001). Patients with a 6-month or greater history of smoking cessation have complication risks similar to those who have never smoked.

Obesity

Decreases in chest wall compliance and in functional residual capacity predispose morbidly obese patients to intra- and postoperative atelectasis (Zerah, 1993). Eichenberger and colleagues (2002) observed that pulmonary changes in these patients may persist for over 24 hours and require aggressive postoperative lung expansion modalities.

Asthma

Well-controlled asthma is not a risk factor for postoperative pulmonary complications. Warner and coworkers (1996) reported that rates of bronchospasm were less than 2 percent in asthmatic patients.

American Society of Anesthesiologist (ASA) Classification

Although this classification was created to help predict perioperative mortality, it also has been shown to assess risks for cardiovascular and pulmonary complications (Wolters, 1996). Table 39-1 summarizes the American Society of Anesthesiologist (ASA) classification and associated rates of postoperative pulmonary complications (Qaseem, 2006).

Table 39-1 American Society of Anesthesiologists (ASA) Classification

ASA Class	Class Definition	Rates of PPCs by Class (%)
I	A normally healthy patient	1.2
II	A patient with mild systemic disease	5.4
III	A patient with systemic disease that is not incapacitating	11.4
IV	A patient with an incapacitating systemic disease that is a constant threat to life	10.9
V	A moribund patient who is not expected to survive for 24 hours with or without operation	NA

NA = not applicable; PPCs = postoperative pulmonary complications.

From Qaseem, 2006, with permission.

HISTORY AND PHYSICAL EXAMINATION

Elements in a pulmonary review of systems that may serve as harbingers of underlying disease include poor exercise tolerance, chronic cough, and otherwise unexplained dyspnea (Smetana, 1999). Physical examination findings of decreased breath sounds, dullness to percussion, rales, wheezes, rhonchi, and a prolonged expiratory phase may signify a nearly sixfold increase in pulmonary complications (Lawrence, 1996; Straus, 2000).

DIAGNOSTIC TESTING

Pulmonary Function Tests and Chest Radiography

In general, pulmonary function tests (PFTs) offer little information during preoperative pulmonary assessment of patients undergoing nonthoracic procedures. Outside of diagnosing chronic obstructive pulmonary disease (COPD), PFTs are not superior to a through history and physical examination (Lawrence, 1996; Qaseem, 2006). However, if the etiology of symptoms, such as exercise intolerance or dyspnea, remains unclear after clinical examination, then PFTs may provide information that will alter perioperative management.

Routine use of chest radiography to assist in perioperative management remains questionable. Compared with a clinical history and

physical examination, preoperative chest radiographs rarely provide evidence to modify therapy (Archer, 1993).

Serum Albumin and Blood Urea Nitrogen

The National Veterans Administration Surgical Quality Improvement Program reported that serum albumin levels of less than 35 mg/dL were significantly associated with increased perioperative pulmonary morbidity and mortality (Arozullah, 2000). Serum albumin's association with morbidity and mortality may be due to confounding by other comorbidity, and thus, is a marker of malnutrition and disease (Goldwasser, 1997). Likewise, serum blood urea nitrogen (BUN) levels greater than 21 mg/dL similarly correlated, but not to the same degree as serum albumin levels.

PREVENTION OF PULMONARY COMPLICATIONS

Lung Expansion Modalities

Techniques aimed at reducing anticipated postoperative decreases in lung volumes can be simple and include postoperative deep breathing exercises, incentive spirometry, and early ambulation. In conscious and cooperative patients, deep breathing effectively improves lung compliance and gas distribution (Chumillas, 1998; Ferris, 1960; Thomas, 1994). With these exercises, a woman is asked to take five sequential deep breaths every hour while awake and hold each for 5 seconds. An incentive spirometer can be added to assist by providing direct visual feedback of her efforts. In addition to deep breathing, early ambulation can enhance lung expansion as well as provide protection from venous thromboembolism. Meyers and associates (1975) demonstrated an increase in functional residual lung capacity of up to 20 percent simply by maintaining an upright posture. Alternatively, formal respiratory physiotherapy may include: (1) chest physical therapy in the form of percussion, clapping, or vibration; (2) intermittent positive-pressure breathing (IPPB); and (3) continuous positive airway pressure (CPAP).

These simple and more formal prophylactic methods are all effective in preventing postoperative pulmonary morbidity, and no method is superior to another. Thomas and colleagues (1994) performed a meta-analysis to compare incentive spirometry (IS), IPPB, and deep breathing exercises (DBEs). In comparison with no therapy, IS and DBEs are superior in preventing postoperative pulmonary complications, and over 50 percent reductions were observed. In addition, no significant differences were noted when comparing IS with DBEs, IS with IPPB, and DBEs with IPPB (Thomas, 1994). However, chest physical therapy, IPPB, and CPAP are more expensive and labor-intensive (Pasquina, 2006). Accordingly, these methods typically are reserved for patients who are unable to perform simpler effort-dependent therapies.

Nasogastric Decompression

Postoperatively, nasogastric tubes (NGTs) are often placed for gastric decompression. However, nasogastric intubation bypasses normal upper and lower respiratory tract mucosal defenses and exposes patients to risks for nosocomial sinusitis and pneumonia. Routine use of an NGT after surgery is associated with increased cases of pneumonia, atelectasis, and aspiration compared with selective use (only in the case of symptomatic abdominal distention or postoperative nausea and vomiting) (Cheatham, 1995). Accordingly, the choice to implement this drainage method should be balanced against respiratory risks.

Cardiac Evaluation

Cardiovascular disease is the leading cause of death in most industrialized countries and contributes significantly to perioperative mortality in patients undergoing cardiac and noncardiac surgery.

RISK FACTORS FOR CARDIAC COMPLICATIONS

Valvular Heart Disease

Careful chest auscultation will reveal findings suspicious for native valvular lesions. Of the most commonly found defects, aortic stenosis carries the highest independent risk factor for perioperative complications (Kertai, 2004). For other lesions, the degree of heart failure and associated cardiac arrhythmias are the best indicators of risk.

Heart Failure

In patients with a history of congestive heart failure, strategies aim to maximize hemodynamic function and minimize postoperative stress (Eagle, 2002). In addition, judicious use of diuretics usually will avoid intraoperative hypovolemia and related hypotension.

Arrhythmias

These are usually symptoms of underlying cardiopulmonary disease or electrolyte abnormalities. Accordingly, preoperative management should focus on correcting the primary process. However, if pacemakers and implantable cardioverter-defibrillators (ICDs) are required for arrhythmia treatment prior to surgery, they typically are placed for the same indications as in nonoperative circumstances (Gregoratos, 2002).

Hypertension

Except in the setting of systolic blood pressures greater than 180 mm Hg and diastolic blood pressures greater than 110 mm Hg, hypertension is not predictive of perioperative cardiac events and should not postpone surgical intervention (Casadei, 2005; Goldman, 1979; Weksler, 2003). If possible, to lower postoperative cardiac complications related to hypertension, blood pressure should be lowered several months prior to an anticipated procedure (Fleisher, 2002). Avoiding hypo- or hypertension intraoperatively with careful postoperative monitoring is recommended. Importantly, intravascular volume expansion, pain, and agitation may exacerbate postoperative hypertension.

DIAGNOSTIC TESTING AND ALGORITHM

Preoperative guidelines have been developed by several groups to help predict the risk of perioperative cardiac complications. The three most prominent lists used in clinical practice are those jointly developed by the American College of Cardiology and the American Heart Association (ACC/AHA), guidelines published by the American College of Physicians (ACP), and the Revised Cardiac Risk Index (RCRI) (American College of Physicians, 1997; Eagle, 2002; Lee, 1999). Each defines major and minor clinical predictors to help guide clinical decision making and offers specific recommendations.

American College of Cardiology and the American Heart Association Guidelines

First published in 1996 and updated in 2002, the ACC/AHA guidelines represent an extensive review of the literature by 12 committee members from various areas of cardiovascular care. This stepwise strategy centers on assessment of three major considerations: clinical predictors, functional capacity, and surgery-specific risk. In general, for gynecologic surgery, cardiac complication risks are greatest with major emergency procedures and operations associated with large intravascular fluid shifts. In contrast, lowest risks are found with brief endoscopic procedures.

Revised Cardiac Risk Index

The Revised Cardiac Risk Index (RCRI) has been tested extensively and offers accurate estimates of cardiac risk (Lee, 1999). The major difference between the RCRI and the ACC/AHA guidelines is the incorporation of exercise capacity in the ACC/AHA tool. Creators of the RCRI suggest that cardiac risk may be overestimated by a patient's noncardiac limitations in function, such as musculo-skeletal pain. Thus, these investigators place greater emphasis on cardiac and vascular disease markers.

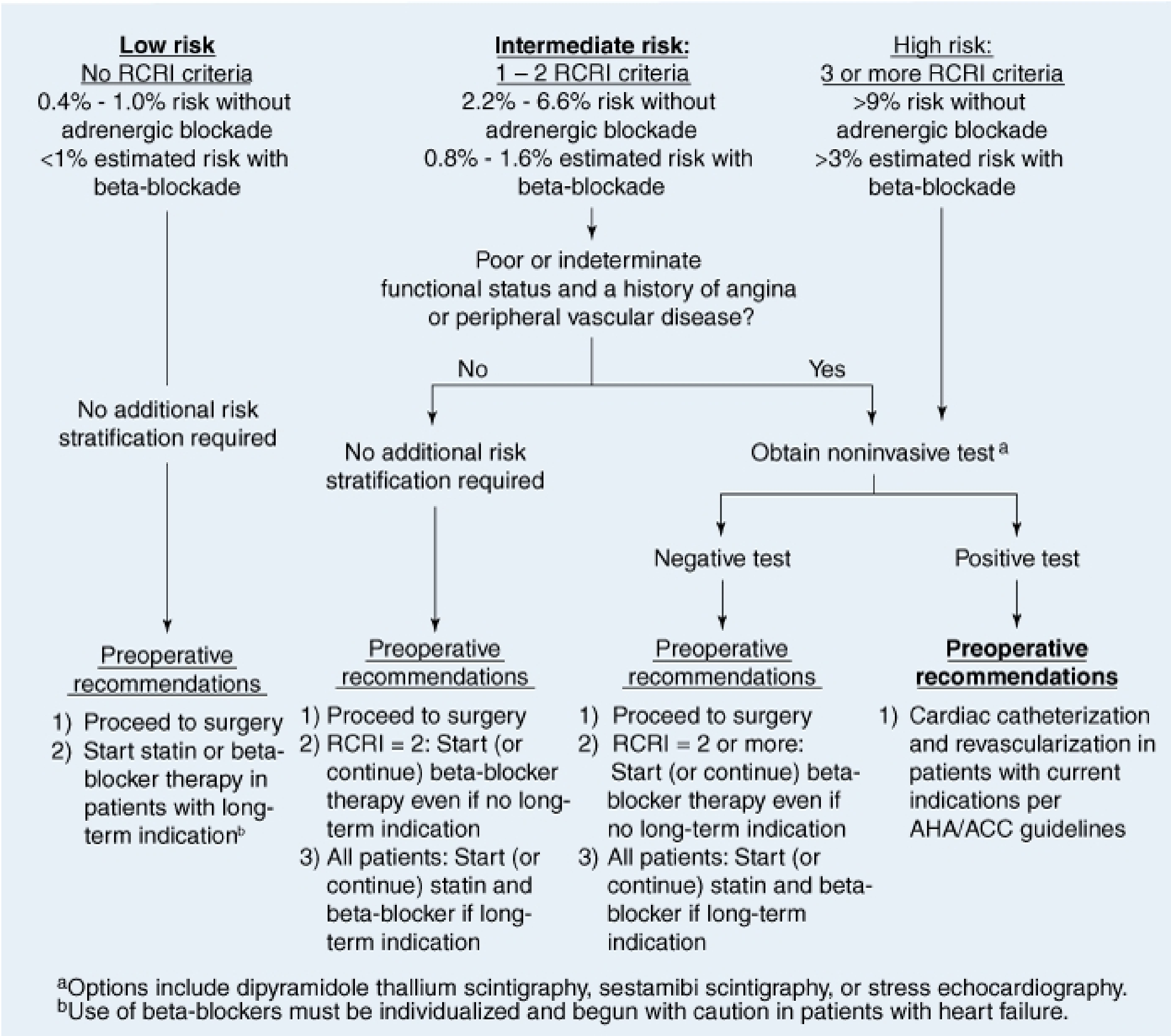
Using the RCRI, an initial evaluation and electrocardiogram (ECG) are completed, and the number of cardiac risk indices from Table 39-2 is calculated. Entry into the algorithm, as shown in Figure 39-2, depends on the number of RCRI criteria (Auerbach, 2006). The use of a dipyramidole thallium scintigraphy, sestamibi scintigraphy, or stress echocardiography as methods of noninvasive cardiac diagnostics should follow ACC/AHA guidelines (Cheitlin, 2003; Falcone, 2003).

Table 39-2 Clinical Factors Important in Assessing Perioperative Cardiac Risk
Revised Cardiac Risk Index (RCRI) Criteria
Patient is at risk if he or she has any one of the following:
• High-risk surgical procedure, defined as thoracic, abdominal, or pelvic vascular (e.g., aorta, renal, mesenteric surgery).
• Ischemic heart disease, defined as: History of myocardial infarction History of/or current angina Use of sublingual nitroglycerin Positive exercise test findings Q waves on ECG Patients who have undergone PTCA or CABG and who have chest pain presumed to be of ischemic origin
• Heart failure, defined as: Left ventricular failure by physical examination History of paroxysmal nocturnal dyspnea History of pulmonary edema S_3 or bilateral rales on physical examination Pulmonary edema on chest radiograph
• Cerebrovascular disease, defined as: History of transient ischemic attack History of cerebrovascular accident
• Insulin-dependent diabetes mellitus
• Chronic renal insufficiency, defined as baseline creatinine ≥ 2.0 mg/dL

CABG = coronary artery bypass graft; ECG = electrocardiogram; PTCA = percutaneous transluminal coronary angioplasty.

From Auerbach, 2006, with permission.

FIGURE 39-2



Algorithm to assess preoperative cardiac risk using Revised Cardiac Risk Index (RCRI) criteria. *(From Auerbach, 2006, with permission.)*

PREVENTION STRATEGIES

Beta-Blocker Drugs

Lindenauer and associates (2005) retrospectively assessed the impact of perioperative beta-blocker use and its effect on in-hospital mortality. In patients with an RCRI of 2 or more, mortality was reduced significantly among patients undergoing major noncardiac procedures who were given beta-blockers perioperatively. Conversely, administration of beta-blockers was potentially harmful in those with low cardiac risk (RCRI of 0 or 1). Outpatient initiation is followed by dosage titration to achieve a resting heart rate of 60 to 65 beats per minute, and therapy is continued for at least 7 days (and ideally 30 days) unless otherwise indicated by pre-existing cardiac disease (Auerbach, 2006; Mukherjee, 2003).

Coronary Revascularization

Diagnostic cardiac catheterization should be considered in high-risk cardiac patients if noninvasive stress testing suggests advanced disease. In such cases, revascularization through coronary artery bypass grafting (CABG) or percutaneous angioplasty offers comparable benefits perioperatively (Hassan, 2001).

Anemia and Cardiac Risk

Anemia has been shown to be an independent risk factor for congestive heart failure (Kannel, 1987). Wu and colleagues (2007) recently found that any degree of hematocrit dysfunction, independent of surgical intervention, increases the risk of postoperative events. They found that the adjusted risk of 30-day postoperative mortality and cardiac morbidity begins to rise when hematocrit levels are above 51 percent and below 39 percent. A study by Silverberg and colleagues (2001) found that correction of even mild anemia (Hgb < 12.5 percent) offered significant improvements in cardiac function. Iron therapy is not a substitution for appropriate cardiac disease treatment, but extrapolated data suggest that maintaining a hemoglobin level above 10 percent is important and reduces perioperative morbidity and mortality.

Hepatic Evaluation

The liver plays a central role in drug metabolism; synthesis of proteins, glucose, and coagulation factors; and excretion of endogenous compounds. Increasing incidences of hepatic disease similarly have increased the number of patients with potential hepatic dysfunction. Accordingly, hepatic function should be assessed if underlying liver disease is suspected.

In patients with suspected liver disease, inquiry should include family histories of jaundice or anemia, recent travel history, exposure to alcohol or other hepatotoxins, and medication use (Patel, 1999). Physical findings suggestive of underlying liver disease include jaundice, scleral icterus, spider angiomas, ascites, hepatomegaly, asterixis, and cachexia.

Of liver diseases, acute and chronic hepatitis are encountered commonly. Postoperative outcome in patients with hepatic disease is primarily determined by the nature and severity of the underlying liver pathology along with the nature of the intended surgical procedure (Sahin, 2007). With acute hepatitis, regardless the cause, there is a high associated perioperative mortality. For this reason, primary management involves supportive care and delay of elective surgical intervention until the acute process has subsided (Patel, 1999). In those with chronic hepatitis, variable levels of hepatic dysfunction are found. Compensated disease carries a low risk of perioperative complications (Sirinek, 1987).

Renal Evaluation

The kidney is involved with excretion of metabolic waste, hematologic processes, and fluid and electrolyte balance. Accordingly, patients with known renal insufficiency should have a serum chemistry panel and complete blood count (CBC) evaluated prior to surgery. Chronic anemia due to renal insufficiency typically will require preoperative administration of erythropoietin or perioperative transfusion. Dialysis patients require intensive pre- and postoperative surveillance for signs of electrolyte abnormalities and fluid overload. Ideally, these patients' volume status and electrolytes (potassium in particular) can be optimized by performing dialysis the day prior to surgery. Additionally, further renal insult is averted by avoiding nephrotoxic agents. Pharmacokinetic consultation may be warranted to adjust other medication dosages because serum levels in these patients may be unpredictable postoperatively.

Hematologic Evaluation

ANEMIA

Preoperative anemia is one of the most common laboratory abnormalities encountered during the preoperative gynecologic surgery evaluation. In the absence of a clear etiology, further evaluation is necessary to correct reversible causes.

The preoperative interview not only should focus on signs of symptomatic anemia (i.e., fatigue, dyspnea with exertion, and palpitations) but also should include identifying risk factors for underlying cardiovascular disease. The physical examination should incorporate thorough pelvic and rectal examinations and stool guaiac testing.

Relevant diagnostic testing for anemic women includes CBC, serum iron level, total iron-binding capacity, ferritin level, reticulocyte

count, and vitamin B_{12} and folate levels. Results from these laboratory studies will dictate preoperative treatment of anemia.

The perioperative decision to transfuse a patient depends in part on the patient's cardiac status. If significant cardiac disease is absent, or if a blood loss of less than 30 percent of total blood volume is anticipated, then an otherwise healthy woman can tolerate a postoperative hemoglobin level of as low as 6 to 7 g/dL (Simon, 1998). A recent randomized controlled trial with patients undergoing elective colorectal surgery found preoperative supplementation of ferrous sulphate 200 mg orally three times daily for 2 weeks significantly reduces the need for postoperative blood transfusions (Lidder, 2007). Conversely, transfusions should be considered if perioperative hypotension and tachycardia fail to respond to volume expansion.

AUTOLOGOUS BLOOD DONATION

Fear of infection from allogenic blood transfusions has lead to the development of autologous transfusion practices. Two of the most popular options include preoperative autologous donation and salvage autologous transfusions, which are discussed in detail in Chapter 40, Fluid Resuscitation and Blood Transfusion (Vanderlinde, 2002).

COAGULOPATHIES

Coagulopathies generally are grouped into two categoriesâ€”inherited and acquired. Disorders involving platelets or clotting factors can be elicited through a careful history and physical examination. A personal history of easy bruising, unexpected amounts of bleeding with minor injury, or lifelong menorrhagia should alert a clinician to the possibility of coagulopathy (see Chap. 8, Coagulopathy). careful review of systems and complete medication list, including herbal preparations, may highlight potential causes. In general, perioperative platelet transfusions typically are required if counts are below 50,000/µL in a patient at risk of bleeding (see Chap. 40, Platelets).

PREOPERATIVE MANAGEMENT OF ORAL ANTICOAGULATION

Women with atrial fibrillation, mechanical heart valves, or recent venous thromboembolism (VTE) are at increase risk for VTE. As a result, these patients typically are prescribed chronic oral warfarin therapy. In addition, surgery inherently increases a patient's risk of developing VTE. Thus, a need for anticoagulation in this group is clear. However this need should be balanced against the risk of bleeding complications from surgery. For these reasons, Kearon and Hirsh (1997) proposed recommendations for the preoperative management of anticoagulants during the period in which the international normalized ratio (INR) is less than 2.0 in patients who use these drugs chronically (Table 39-3).

Table 39-3 Recommendations for Preoperative and Postoperative Anticoagulation in Patients WHO Are Taking Oral Anticoagulants[a]

Indication	Before Surgery	After Surgery
Acute venous thromboembolism		
• Month 1	IV heparin[b]	IV heparin[b]
• Months 2 and 3	No change[c]	IV heparin
Recurrent venous thromboembolism[d]	No change[c]	SC heparin
Acute arterial embolism		
• Month 1	IV heparin	IV heparin[e]
Mechanical heart valve	No change[c]	SC heparin
Nonvalvular atrial fibrillation	No change[c]	SC heparin

[a] IV heparin denotes intravenous heparin at therapeutic doses, and SC heparin denotes subcutaneous unfractionated or low-molecular-weight heparin in doses recommended for prophylaxis against venous thromboembolism in high-risk patients.

[b] A vena caval filter should be considered if acute venous thromboembolism has occurred within 2 weeks or if the risk of bleeding during intravenous heparin therapy is high.

[c] If patients are hospitalized, subcutaneous heparin may be administered, but hospitalization is not recommended solely for this purpose.

[d] The term refers to patients whose last episode of venous thromboembolism occurred more than 3 months before evaluation but who require long-term anticoagulation because of a high risk of recurrence.

[e] Intravenous heparin should be used after surgery only if the risk of bleeding is low.

From Kearon, 1997, with permission.

After an acute VTE, the recurrence risk without anticoagulation is between 40 and 50 percent. However, the risk of recurrent disease drops significantly after 3 months of warfarin therapy (Coon, 1973; Kearon, 1997; Levine, 1995). Specifically, a delay in surgery and continued warfarin therapy for an additional 2 to 3 months drop the recurrence risk to 5 to 10 percent and avoid a need for preoperative heparin (Kearon, 1997; Levine, 1995). Thus, in those with recent VTE, a surgical delay, if feasible, may be advantageous and should be considered.

Following temporary cessation of oral anticoagulation therapy, surgery can be performed safely once the INR reaches 1.5 (Tinker, 1978; White, 1995). If the INR is between 2.0 and 3.0, approximately 4 days are required for the ratio to reach 1.5. After postoperative reinstitution of anticoagulation, approximately 3 days are required to reach therapeutic levels (Harrison, 1997; White, 1995). Importantly, postoperative heparin should not be restarted until at least 12 hours after major surgery and longer if there is evidence of bleeding.

Endocrine Evaluation

The pathophysiologic stress of surgery can exacerbate endocrine conditions such as thyroid dysfunction, diabetes mellitus, and adrenal insufficiency.

HYPERTHYROIDISM AND HYPOTHYROIDISM

Both hyper- and hypothyroidism have anesthetic and metabolic derangements unique to each disease state. Nevertheless, management goals for both aim to achieve a euthyroid state before surgery.

Hyperthyroidism carries the risk of developing thyroid storm perioperatively. Moreover, airway compromise is a risk in those with goiter, and during physical examination, special attention should be given to evaluating for tracheal deviation. In addition to thyroid function tests, an ECG and serum electrolyte levels can help to predict signs of pre-existing metabolic stress. Patients should be encouraged to maintain their usual medications at prescribed dosages until the day of surgery.

Newly diagnosed hypothyroidism generally does not require preoperative therapy except in cases of severe disease with signs of cardiac depression, electrolyte irregularities, and hypoglycemia.

DIABETES MELLITUS

Long-term complications of diabetes mellitus may include vascular, neurologic, cardiac, and renal dysfunction. Thus, a vigilant preoperative risk assessment of these comorbidities in patients with diabetes mellitus is essential. In addition, increased postoperative morbidity has been linked with poor preoperative glycemic control. Specifically, glucose levels of greater than 200 mg/dL and hemoglobin A_{1C} levels of greater than 7 percent are both associated with significantly increased rates of postoperative wound infection (Dronge, 2006; Trick, 2000).

At minimum, diabetic patients undergoing major surgical procedures would benefit from three diagnostic testsâ€”serum electrolyte levels, urinalysis, and an ECGâ€”to screen for metabolic disturbances, undiagnosed nephropathy, and unrecognized cardiac ischemia in the form of abnormal Q waves, respectively.

In general, stress induced by surgery and anesthesia can lead to elevations in catecholamine levels, relative insulin deficiency, and hyperglycemia (Devereaux, 2005). Although glycemic responses may vary with surgery, overt hyperglycemia should be avoided to minimize postoperative complications related to dehydration, electrolyte abnormalities, diminished wound healing, and even ketoacidosis in type I diabetics (Jacober, 1999). However, fluctuations in oral intake and metabolic need make optimal glycemic

control labor-intensive. Moreover, clear evidence for glucose targets are lacking. As a result, most providers aim for glucose readings below 200 g/dL (Table 39-4) (Finney, 2003; Garber, 2004). Table 39-5 and Figure 39-3 summarize perioperative recommendations set forth by Jacober and colleagues (1999) based on disease severity.

Table 39-4 Sliding-Scale Insulin Order Example[a]

Blood Glucose, mmol/L (mg/dL)[b]	Increment Formula	Calculation	Short-Acting Insulin, units
0â€“11.0 (0â€“200)	0	0	0
11.1â€“14.0 (201â€“250)	1 x (TDI/30)	1 x (120/30)	4
14.1â€“17.0 (251â€“300)	2 x (TDI/30)	2 x (120/30)	4
17.1â€“20.0 (301â€“350)	3 x (TDI/30)	3 x (120/30)	12
20.1â€“23.0 (251â€“400)	4 x (TDI/30)	1 x (120/30)	16
23.1â€“26.0 (401â€“450)	5 x (TDI/30)	5 x (120/30)	20
>26.0 (>450)	Call physician	Call physician	Call physician

[a] Example uses a preoperative total daily insulin dose (TDI) of 120 units.

[b] For convenience, conversions of millimoles per liter to milligrams per deciliter are approximate.

From Jacober, 1999, with permission.

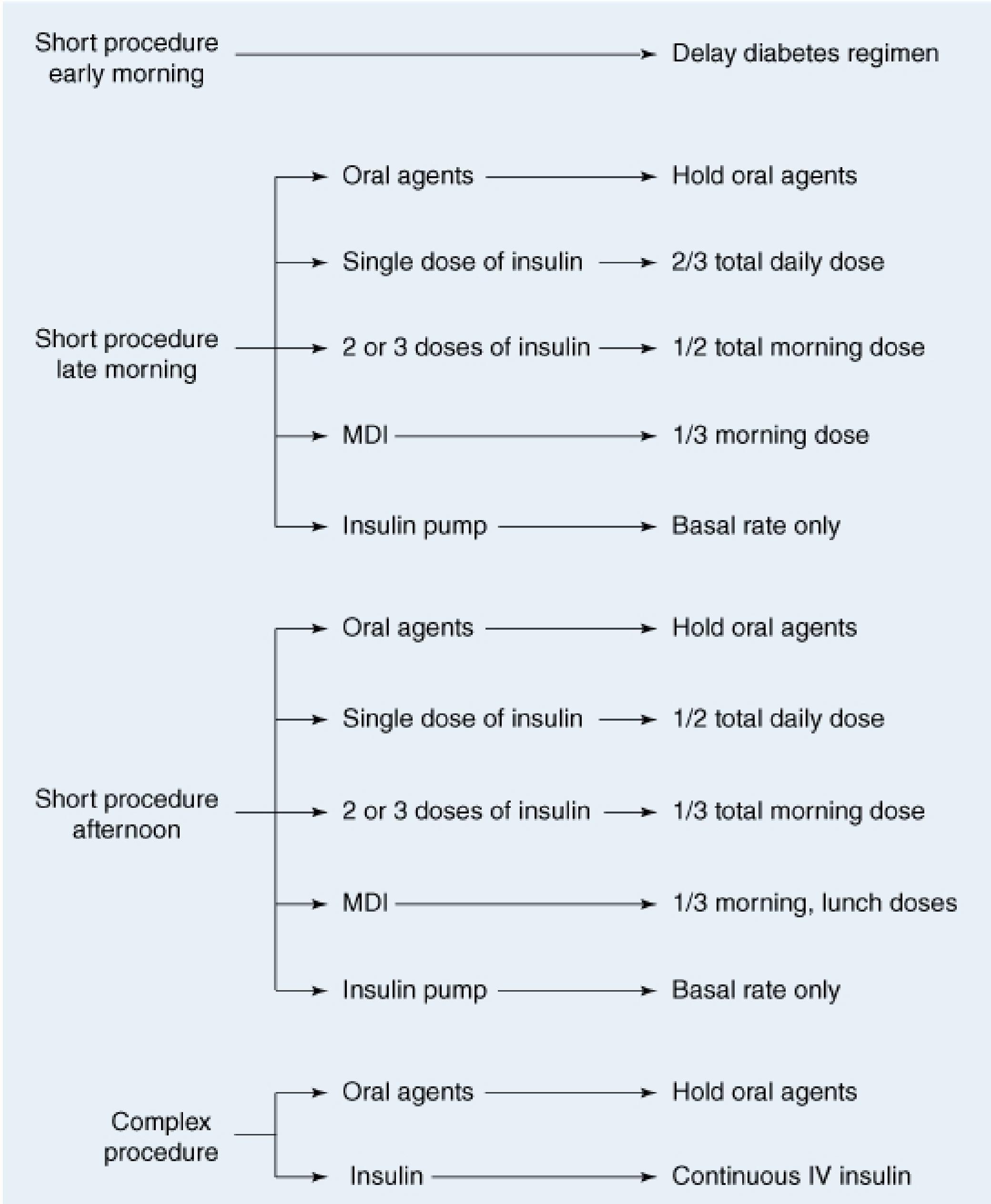
Table 39-5 Perioperative Management of Diabetes Mellitus by Disease Type

Disease	Preoperative Management	Postoperative Management
Type 2 DM treated with diet alone	No additional care with PRN subcutaneous regular insulin for AM hyperglycemia	PRN subcutaneous regular insulin
Type 2 DM treated with oral hypoglycemic agents	Discontinue all agents on the day of surgery	Supplemental subcutaneous insulin until return of normal diet, at which time preoperative therapy can be reinstituted
Type 1or 2 DM treated with insulin	See Figure 39-3	Sliding-scale insulin (Table 39-4)

DM = diabetes mellitus.

Adapted from Jacober, 1999, with permission.

FIGURE 39-3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Perioperative management recommendations for surgical patients with diabetes mellitus. IV = intravenous; MDI = multiple doses of short-acting insulin. *(From Jacober, 1999, with permission.)*

ADRENAL INSUFFICIENCY

Perioperatively, hypotension can result from inadequacy of the hypothalamic-pituitary-adrenal (HPA) axis due to secondary suppression from chronic steroid use. Despite this physiologic understanding, controversy surrounds steroid supplementation during the perioperative period.

Corticosteroid users who undergo minor surgical procedures or who use lower steroid doses (less than 5 mg prednisone per day for no more than 2 weeks within the past year) generally are assumed not to be at risk for adrenal suppression. Therefore, additional steroid therapy is not recommended. However, those taking 5 to 20 mg prednisone per day for more than 3 weeks may be at risk for HPA axis suppression. In these patients, an adrenocorticoticotropic hormone (ACTH) stimulation test can verify adrenal suppression and identify those who may benefit from perioperative steroid supplementation.

The value of perioperative steroid supplementation remains an area of chronic debate (Bromberg, 1991). For example, patients who took at least 7.5 mg prednisone daily for several months with secondary adrenal insufficiency documented by ACTH testing were randomized to placebo versus high-dose cortisol supplementation. Simply continuing the patient's usual daily dose of steroids perioperatively resulted in no increase in hypotension or other perioperative signs of adrenal insufficiency (Glowniak, 1997). If an additional steroid dose is administered, patients should be titrated down to their daily replacement within 48 hours of surgery. Table 39-6 summarizes strategies for steroid supplementation based on surgical stress.

Table 39-6 Guidelines for Adrenal Supplementation Therapy[a]

Medical or Surgical Stress	**Corticosteroid Dosage**
Minor	
Inguinal hernia repair	25 mg hydrocortisone or 5 mg methylprednisolone IV on day of procedure only
Colonoscopy	
Mild febrile illness	
Mildâ€“moderate nausea/vomiting	
Gastroenteritis	
Moderate	
Open cholecystectomy	50â€“75 mg hydrocortisone or 10â€“15 mg methylprednisolone IV on day of procedure Taper quickly over 1â€“2 days to usual dose
Hemicolectomy	
Significant febrile illness	
Pneumonia	
Severe gastroenteritis	
Severe	
Major cardiothoracic surgery	100â€“150 mg hydrocortisone or 20â€“30 mg of methylprednisolone IV on day of procedure Rapid taper to usual dose over next 1â€“2 days
Whipple procedure	
Liver resection	
Pancreatitis	
Critically ill	
Sepsis-induced hypotension or	50â€“100 mg hydrocortisone IV q6â€“8h or 0.18 mg/kg/h as a continuous infusion and 50 µg/d

shock	fludrocortisone until shock resolves May take several days to a week or more Then gradually taper, following vital signs and serum sodium

[a] Patients receiving 5 mg/d or less of prednisone should receive their normal daily replacement but do not require supplementation. Patients who receive greater than 5 mg/d of prednisone should receive the preceding therapy in addition to their maintenance therapy.

From Coursin, 2002, with permission.

DIAGNOSTIC TESTING GUIDELINES

In the absence of a clinical indication, a routine panel of preoperative tests does not enhance the safety or quality of care. Roizen and colleagues (2000) found that nearly half the abnormalities seen on routine preoperative testing were ignored by clinicians. Moreover, multiple studies have documented the inefficiency of hematologic tests to yield clinically significant diagnoses (Kaplan, 1985; Korvin, 1975). Most important, diagnostic testing has not been shown to outperform a clinical history and physical examination (Rucker, 1983). Thus, in the absence of changes in clinical status, diagnostic tests found to be normal 4 to 6 months prior to surgery may be used as "preoperative tests". In patients managed this way, MacPherson and colleagues (1990) found that fewer than 2 percent had significant changes over the course of 4 months.

Pregnancy Exclusion

Pregnancy should be identified prior to surgery. Although many indicated gynecologic procedures may be performed during pregnancy, re-evaluation of the need and the approach to many operations are affected by concurrent pregnancy.

Several preventive steps can avoid procedures in women with early, undiagnosed pregnancies. Providing contraception well in advance of surgery, scheduling surgery in the follicular phase, and preoperative serum beta human chorionic gonadotropin (β-hCG) testing are effective methods to prevent or detect early pregnancy concurrent with surgery (American College of Obstetricians and Gynecologists, 2003).

Pap Smear Screening

As with pregnancy, cervical neoplasia may alter the need or approach to surgical correction of a gynecologic problem. For example, simple (Type 1) hysterectomy performed to treat a benign gynecologic condition will be inadequate treatment to cure most stages of cervical cancer (see Chap. 30, Papanicolaou Smear). Accordingly, women should have current Pap smear screening prior to surgery.

INFORMED CONSENT

Obtaining informed consent is a process and not merely a medical record document (Kondziolka, 2006; Lavelle-Jones, 1993; Nandi, 2000). This conversation between a clinician and patient should enhance the woman's awareness of her diagnosis and contain discussion of medical and surgical care alternatives, procedure goals and limitations, and surgical risks. Written documentation serves as a historical record of the patient's understanding and agreement.

Despite a clinician's recommendations, an informed patient may decline a particular intervention. A woman's decision-making autonomy must be respected, and the clinician should document informed refusal in the medical record. Appropriate documentation should include: (1) the patient's refusal to consent to the recommended intervention, (2) notation that the value of the intervention has been explained to the patient, (3) the patient's reasons for refusal, and (4) a statement describing the health consequences as described to the patient (American College of Obstetricians and Gynecologists, 2004).

SPECIAL CONSIDERATIONS

Surgical Site Infection Prophylaxis

Antibiotic prophylaxis can reduce hospital-acquired infections significantly following gynecologic surgery. Decisions regarding the choice, timing, and duration of antibiotic prophylaxis are guided by the intended procedure and the anticipated organisms to be encountered. Prophylaxis is summarized in Table 39-7 and discussed in Chapter 3, Clean Wounds.

Table 39-7 Antimicrobial Prophylactic Regimens by Procedure

Procedure	Antibiotic	Dose
Vaginal/abdominal hysterectomy[a]	Cefazolin	1- or 2-g single dose IV
	Cefoxitin	2-g single dose IV
	Metronidazole[b]	1-g single dose IV
	Tinidazole[b]	2-g single oral dose (4â€"12 hours before surgery)
Laparoscopy	None	
Laparotomy	None	
Hysteroscopy	None	
Hysterosalpingogram	Doxycycline[c]	100 mg orally twice daily for 5 days
IUD insertion	None	
Endometrial biopsy	None	
Induced abortion/D&C	Doxycycline	100 mg orally 1 hour before procedure and 200 mg orally after procedure
	Metronidazole	500 mg orally twice daily for 5 days
Urodynamic testing	None	

IV = intravenously; IUD = intrauterine device; D&C = dilatation and curettage.

[a] A convenient time to administer antibiotic prophylaxis is just before induction of anesthesia.

[b] Antimicrobial agents of choice in women with a history of immediate hypersensitivity to penicillin.

[c] If hysterosalpingogram demonstrated dilated fallopian tubes. No prophylaxis is indicated for a study without dilated tubes.

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Subacute Bacterial Endocarditis Prophylaxis

Sufficient evidence exists regarding the association between bacteremia and postprocedural endocarditis (Durack, 1995; van der Meer, 1992). Despite a lack of randomized trials, prevention of this highly morbid complication with preoperative antibiotics is justified in patients at risk of developing disease (Table 39-8) (Dajani, 1997; Seto, 2007). The mechanism behind the prevention of subacute bacterial endocarditis (SBE) is unclear, but evidence suggests that antibiotics alter bacterial adhesion to heart valves (Moreillon, 1986).

Table 39-8 Subacute Bacterial Endocarditis Prophylaxis by Surgical Procedure

Cardiac Conditions Associated with Endocarditis	**Endocarditis Prophylaxis by Surgical Procedure**
Endocarditis prophylaxis recommended	**Endocarditis prophylaxis recommended**
High-risk category	Gastrointestinal tract[a]
Prosthetic cardiac valves, including bioprosthetic and homograft valves	Surgical operations that involve intestinal mucosa
Previous bacterial endocarditis	Genitourinary tract
Complex cyanotic congenital heart disease (e.g., single-ventricle states, transposition of the great arteries, tetralogy of Fallot)	Cystoscopy
Surgically constructed systemic pulmonary shunts or conduits	Urethral dilation
Moderate-risk category	Other genitourinary procedures only in presence of infection
Most other congenital cardiac malformations (other than those listed above and below)	**Endocarditis prophylaxis not recommended**
Acquired valvar dysfunction (e.g., rheumatic heart disease)	Genitourinary tract
Hypertrophic cardiomyopathy	Vaginal hysterectomy[b]
Mitral valve prolapse with valvar regurgitation, thickened leaflets, or both	Urethral catheterization
Endocarditis prophylaxis not recommended	Uterine dilation and curettage
Negligible-risk category (risk no greater than that of the general population)	Therapeutic abortion
Isolated secundum atrial septal defect	Sterilization procedures
Surgical repair of atrial septal defect, ventricular septal defect, or patent ductus arteriosus (without residua beyond 6 months)	Insertion or removal of intrauterine device

[a] Prophylaxis is recommended for high-risk patients; option for medium-risk patients.

[b] Prophylaxis is option for high-risk patients.

From American College of Obstetricians and Gynecologists, 2006, and Dajani, 1997, with permissions.

Candidates for SBE prophylaxis are classified by their underlying cardiac disease and the degree of bacteremia anticipated from the planned surgical procedure. The American Heart Association identifies cardiac lesions as negligible, moderate, or high-risk for developing postprocedural infection (Dajani, 1997). For those at risk, antibiotics should be administered prior to the procedure. Recommended antibiotic prophylaxis guidelines endorsed by the American Heart Association and the American College of Obstetricians and Gynecologists are summarized in Table 39-9.

Table 39-9 Endocarditis Prophylaxis Regimens for Genitourinary and Gastroinestinal Procedures		
Situation	**Agents**	**Regimen**
High-risk patients	Ampicillin plus gentamicin	Adults: ampicillin 2.0 g IM or IV plus gentamicin 1.5 mg/kg (not to exceed 120 mg) within 30 min of starting procedure; 6 h later, ampicillin 1 g IM/IV or amoxicillin 1 g orally
High-risk patients allergic to ampicillin/amoxicillin	Vancomycin plus gentamicin	Adults: vancomycin 1.0 g IV over 1â€"2 h plus gentamicin 1.5 mg/kg IV/IM (not to exceed 120 mg); complete injection/infusion within 30 min of starting procedure
Moderate-risk patients	Amoxicillin or ampicillin	Adults: amoxicillin 2.0 g orally 1 h before procedure, or ampicillin 2.0 g IM/IV within 30 min of starting procedure
Moderate-risk patients allergic to ampicillin/amoxicillin	Vancomycin	Adults: vancomycin 1.0 g IV over 1â€"2 h; complete infusion within 30 min of starting procedure

IM = intramuscular; IV = intravenous.

From Dajani, 1997, with permission.

Gastrointestinal Bowel Preparation

Surgical dogma drives the use of mechanical bowel preparation as a means to prevent postoperative complications (Bucher, 2004). Studies conducted prior to the routine administration of antibiotic prophylaxis argued that bowel cleansing prior to colorectal surgery improved bowel handling, prevented anastomosis disruption with the passage of hard feces, and decreased fecal and bacterial loads. Thus, bowel cleansing was thought to reduce wound infection rates (Barker, 1971; Nichols, 1971).

Multiple recent studies, however, question the routine use of mechanical bowel preparations (Guenaga, 2003; Platell, 1998). Ram and co-workers (2005) prospectively randomized 329 patients undergoing elective large bowel resection to see whether routine mechanical bowel preparation reduced postoperative morbidity and mortality, including anastomotic breakdown and wound infections. They found no differences. Similar results have been found following gynecologic and urologic procedures (Muzii, 2006; Shafii, 2002). Moreover, a recent report contradicts the belief that mechanical bowel preparation decreases microbial contamination of the peritoneal cavity and subcutis after elective open-colon surgery (Fa-Si-Oen, 2005). It is not surprising to find that patients who do not have a mechanical bowel preparation are more satisfied and experience shorter times to their first postoperative bowel movement (Jung, 2007).

Although its routine use should be limited, mechanical bowel preparation is often preferred for many female pelvic reconstructive procedures involving the posterior vaginal wall and anal sphincter. In these cases, evacuation of rectal stool provides additional operating space and undistorted anatomy. Moreover, preoperative evacuation typically delays stooling and allows initial healing following sphincteroplasty. Other instances in which mechanical bowel preparation may be recommended include those in which the entire colon may be palpated during surgery for evaluation of tumor involvement. Table 39-10 provides a summary of various commercially available preparations used commonly for bowel preparation (Valantas, 2004).

Table 39-10 Colon Cleansing Preparation Methods

Diet and Cathartics	
Diet	Clear liquids for 3 days or a diet designed to leave a minimal colonic fecal residue for 1â€“3 days
Cathartics	Extract of senna fruit (X-Prep) 240 mL or magnesium citrate 240 mL
Additional cathartic	Bisacodyl 20 mg orally and suppositories
Enemas	Sodium phosphate or tap water
Kits	Liqui Prep, Nutra Prep, LoSo Prep System
Gut Lavage Methods	
Polyethylene glycolâ€“electrolyte lavage solution (PEG-ELS)	
Sodium sulfate and polyethylene glycol (PEG) GoLYTELY, CoLyte	
Sulfate-freeâ€“electrolyte lavage solution (SF-ELS)	
PEG without sulfate NuLYTELY	
Reduced volume with bisacodyl or magnesium citrate Half Lytely	
Phosphate Preps	
Oral sodium phosphate	
Fleet's Phosphosoda	
Phosphate Tablets	
Visicol	

From Valantas, 2004, with permission.

Thromboembolism

PREVENTION

Venous thromboembolism (VTE) is a general category used to describe venous clot formation and includes the more specific entities of deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE). Prophylaxis against VTE ranks in the top 10 patient safety practices recommended by the Agency for Healthcare Research and Quality (AHRQ) and the National Quality Forum (Michota, 2006). In the United States alone, it is estimated that the incidence of DVT approaches 450,000, with an additional 350,000 nonfatal PTE and 250,000 fatal PTE (Bick, 2002). National recommendations for prophylaxis against VTE follow a risk-based approach. The American College of Obstetricians and Gynecologists (2007) provides a summary of VTE risk factors pertinent during gynecologic surgery and successful prevention strategies of DVT/PTE (Table 39-11).

Table 39-11 Levels of Thromboembolism Risk in Surgical Patients Without Prophylaxis					
	DVT, %		PE, %		Successful Prevention Strategies
Level of Risk	**Calf**	**Proximal**	**Clinical**	**Fatal**	
Low risk	2	0.4	0.2	<0.01	No specific prophylaxis; early and "aggressive" mobilization
Minor surgery in patients <40 yr with no additional risk factors					
Moderate risk	10â€“20	2â€“4	1â€“2	0.1â€“0.4	LDUH (q12h), LMWH (≤ 3400 units daily), GCS, or IPC
Minor surgery in patients with additional risk factors Surgery in patients aged 40â€“60 yr with no additional risk factors					
High risk	20â€“40	4â€“8	2â€“4	0.4â€“1.0	LDUH (q8h), LMWH (≤ 3400 units daily), or IPC
Surgery in patients >40â€“60 yr with additional risk factors (prior VTE, cancer, molecular hypercoagulability)					
Highest risk	40â€“60	10â€“20	4â€“10	0.2â€“5	LMWH (>3400 units daily), fondaparinux, oral VKAs (INR 2â€“3), or IPC/GCS + LDUH/LMWH Consider continuing prophylaxis for 2â€“4 weeks after discharge
Surgery in patients with multiple risk factors (age >40 yr, cancer, prior VTE, or molecular hypercoagulability)					
Hip or knee arthroplasty,					
HFS Major trauma, SCI					

DVT = deep vein thrombosis; GCS = graduated compression stockings; HFS = hip fracture surgery; INR = international normalized ratio; IPC = intermittent pneumatic compression; LDUH = low-dose unfractionated heparin; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; SCI = spinal cord injury; VKAs = vitamin K antagonists; VTE = venous thromboembolism.

From Geerts, 2004, and American College of Obstetricians and Gynecologists, 2007, with permission.

Hormone Discontinuation

Of risks, hormone use is one factor that can be modified prior elective surgery. Combined oral contraceptive pills (COCs) induce hypercoagulable changes that are reversed if COCs are stopped at least 6 weeks prior to surgery (Robinson, 1991; Vessey, 1986). To balance the risk of unintended pregnancy in women halting COCs, a suitable alternative is recommended with clear instructions on use.

Postmenopausal hormone replacement therapy (HRT) appears also to increase the incidence of postoperative VTE. Grady and colleagues (2000) estimate a fivefold increase in the risk of developing a venous thrombotic event during the first 90 days after inpatient surgery. Thus, women should be counseled appropriately on this additional postoperative risk, but the value and duration of HRT cessation to negate this increased risk are unclear.

Prophylaxis Options

Various modalities for prophylaxis exist. Early ambulation, though encouraged after surgery, is not regarded as a primary strategy

for DVT prophylaxis (Michota, 2006). Graded compression stockings (TED hose), when used in conjunction with other methods of prophylaxis, offer additional benefit (Amaragiri, 2000). Intermittent pneumatic compression (IPC) works primarily by improving venous flow. It appears to be effective in moderate- and high-risk patients if initiated prior to the induction of anesthesia and continued until patients are fully ambulatory (Clarke-Pearson, 1993; Geerts, 2004). Pharmacologic methods of VTE prophylaxis include low-dose unfractionated heparin, low-molecular-weight heparin, and new classes of medications such as factor Xa inhibitors.

DIAGNOSIS AND TREATMENT OF THROMBOEMBOLISM

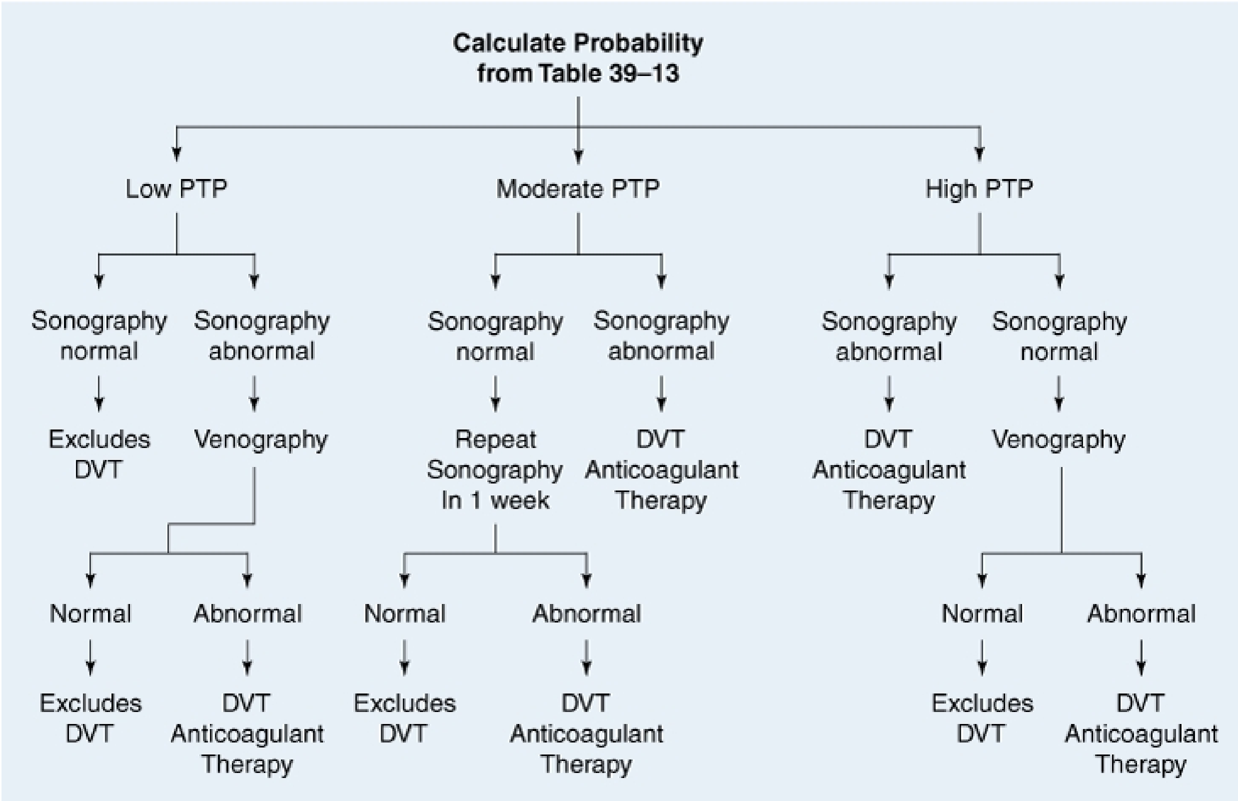
If VTE is suspected, evaluation begins with clinical examination and estimation of the woman's likelihood for disease. Wells and colleagues (1995) published one of the most widely used clinical prediction algorithms (Fig. 39-4 and Table 39-12). When indicated, duplex sonography is highly sensitive for detecting proximal DVT, with a false-negative rate of 0 to 6 percent (Gottlieb, 1999). For PTE, clinicians continue to use ventilation-perfusion (VQ) scanning and helical computed-tomographic (CT) scanning as alternatives to the invasive "gold standards"â€”pulmonary angiography or contrast venography.

Table 39-12 Pretest Probability for Deep Vein Thrombosis

Clinical Probability
High ≥3 major points and no alterative diagnosis ≥2 major points and ≥2 minor points + no alternative diagnosis
Low 1 major point + ≥2 minor points + has an alterative diagnosis 1 major point + ≥1 minor point + no alterative diagnosis 0 major points + ≥3 minor points + has an alterative diagnosis 0 major points + ≥2 minor points + no alterative diagnosis
Moderate All other combinations

From Wells, 1995, with permission.

FIGURE 39-4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Algorithm for evaluation of suspected deep vein thrombosis (DVT). PTP = pretest probability. *(From Wells, 1995, with permission.)*

Acute management of VTE involves anticoagulation with intravenous unfractionated heparin or subcutaneous low-molecular-weight heparin. After achieving adequate anticoagulation, oral vitamin K antagonists such as warfarin are initiated. Therapy duration is dictated by clinical circumstance and typically is administered for: (1) 3 to 6 months following a first idiopathic DVT, (2) 6 months for PTEs, and (3) indefinitely for those with a thrombophilic condition or a second VTE.

Postoperative Nausea and Vomiting

This is one of the most common complaints following surgery, and its incidence ranges from 30 to 70 percent in high-risk patients (Moller, 2002). Those at risk for postoperative nausea and vomiting (PONV) include females, nonsmokers, those with a history of motion sickness or PONV, those with extended surgeries, and those undergoing laparoscopic or other gynecologic surgery (Apfelbaum, 2003).

A multimodal approach to prevention is recommended (Apfel, 2004). Currently, combinations of 4 to 8 mg dexamethasone prior to anesthesia induction are followed by less than 1 mg droperidol and 4 mg ondansetron toward the end of surgery. This pretreatment significantly reduces symptoms by 25 percent. However, if symptoms develop within 6 hours of surgery, antiemetics from a different pharmacologic class than previously administered should be considered (Habib, 2004). Persistent nausea may benefit from combining agents from different classes (Table 39-13).

Table 39-13 Commonly Used Medications for Nausea and Vomiting

Class/Medication	Usual Dosage	Route(s)	Adverse Effects
Anticholinergic			
Scopolamine (Transderm Scop)	1 patch every 3 d	Transdermal	Dry mouth, drowsiness, impaired eye accommodation
Antihistamines			
Diphenhydramine (Benadryl)	25â€“50 mg q4â€“6h	IM, IV, PO	Sedation, dry mouth, constipation, blurred vision, urinary retention
Hydroxyzine (Atarax, Vistaril)	25â€“100 mg q6h	IM, PO	
Meclizine (Antivert)	25â€“50 mg q6h	PO	
Promethazine (Phenergan)	12.5â€“25 mg q4â€“6h	IM, IV, PO, PR	
Benzamides			
Metoclopramide (Reglan)	5â€“15 mg q6h	IM, IV, PO	Sedation or agitation, diarrhea, extrapyramidal effects, hypotension
Trimethobenzamide (Tigan)	250 mg q6â€“8h	IM, PO, PR	
Benzodiazepines			
Lorazepam (Ativan)[a]	0.5â€“2.5 mg q8â€“12h	IM, IV, PO	Sedation, amnesia, respiratory depression, blurred vision, hallucinations
Corticosteroids			
Dexamethasone (Decadron)[a]	4 mg q6h	IM, IV, PO	GI upset, anxiety, insomnia, hyperglycemia
Phenothiazines			
Prochlorperazine (Compazine)	5â€“10 (25 PR) mg q6h	IM, IV, PO, PR	Sedation, extrapyramidal effects, cholestatic jaundice, hyperprolactinemia
5-HT3 Serotonin Antagonists			
Ondansetron (Zofran)	8 mg q8h	IV, PO	Headache, fever, arrhythmias, ataxia, somnolence or nervousness, elevated hepatic transaminases
Granisetron (Kytril)	2 mg per 24 h	IV, PO	
Dolasetron (Anzemet)	100 mg per 24 h	IV, PO	

GI = gastrointesintal; HT = hydroxytryptamine; IM = intramuscular; IV = intravenous; PO = orally; PR = per rectum.

[a] Not FDA approved for this indication.

From Miser, 2006, with permission.

POSTOPERATIVE CONSIDERATIONS

Thorough preoperative planning, awareness of common postoperative complications, and vigilance to details will ensure successful convalescence for most patients.

Postoperative Orders

Postoperative orders provide instruction regarding support of each organ system while normal function is gradually reestablished. Although orders are customized for each woman, goals are common among all surgical patientsâ€”resuscitation, pain control, and resumption of daily activities. Table 39-14 offers a template for both inpatient and outpatient postoperative orders.

Table 39-14 Typical Postoperative Orders (Inpatient and Outpatient)

Postoperative Orders (Inpatient)	Postoperative Orders (Outpatient)
Admit to: recovery room/assigned hospital floor/attending physician's name	Admit to: recovery room; transfer to DSU when cleared by anesthesia
Diagnosis: s/p what surgical procedure	Diagnosis: s/p what surgical procedure
Condition: stable	Condition: stable
Vital signs: q1h $\times$ 4, q2h $\times$ 2, then q4h	VS per routine
Activity: bed rest	Allergies: NKDA
Allergies: NKDA	Bed rest until A&A, then activity ad lib
Notify MD for: T > 101Â°F; BP > 160/110, <90/60; P > 130; RR > 30, <10; UOP < 120 mL/4 h; acute changes	NPO until A&A, then clear liquids
Diet: NPO except ice chips	IV fluids: LR at 125 mL/h until tolerating PO, then D/C IV
IV fluids: LR at 125/h	Notify MD for: T > 101Â°F; BP > 160/110, <90/60; P > 130; RR > 30, <10; acute changes
Special: Strict I/Os Turn, cough, deep breath q1h while awake IS to BS, q1h while awake Foley to gravity SCD hose to pump	D/C patient home when A&A, cleared by anesthesia, taking PO, ambulating, & able to void
Medications: 1. PCA orders: mix 30 mg MSO_4 in 30 mL NS; load 4â€“6 mg, then IV q6min on demand; lockout 20 mg in 4 hours	F/U at ____________ clinic in _____ weeks

2. Phenergan 25 mg IV q6h prn N/V 3. Â±Toradol 30 mg IM q6h x 24 h (only if Cr is okay)	
Labs: H&H in am (or that afternoon if necessary)	Write any necessary prescriptions

A&A = awake and alert; BS = bedside; Cr = creatinine; D/C = discontinue; DSU = day surgery unit; F/U = follow-up; H&H = hemoglobin and hematocrit; I/Os = input and output; IM = intramuscular; IS = incentive spirometry; IV = intravenous; LR = lactated Ringer's; MSO_4 = morphine sulfate; NKDA = no known drug allergies; NPO = nil per os; NS = normal saline; N/V = nausea and vomiting; PCA = patient-controlled analgesia; PO = per os; RR = respiratory rate; SCD = sequential compression device; s/p = status post; UOP = urine output; VS = vital signs.

Pain Management

Postoperative pain management remains undervalued, and many patients continue to experience pain after surgery. A recent survey by Apfelbaum and colleagues (2003) revealed that more than 85 percent of respondents following surgery have moderate to severe pain. Poor pain control leads to decreased satisfaction with care, prolonged recovery time, increased use of health care resources, and increased health care costs (Joshi, 2005).

NONOPIOID TREATMENT OPTIONS

The two major classes of nonopioid therapies are acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs). In general, these drugs are well tolerated and carry a low risk of serious side effects. However, acetaminophen can be toxic to the liver in high doses. Thus, dosages greater than 4,000 mg/d should be avoided, especially if providing combination therapy with oral opioids and nonopioid drugs. If given preoperatively, NSAIDs reduce postoperative pain, lower the amount of required opiates, and decrease the incidence of PONV by as much as 30 percent (Adachi, 2007; Akarsu, 2004; Chan, 1996; Mixter, 1998).

OPIOID TREATMENT OPTIONS

Despite the common side effects that all opiates shareâ€"respiratory depression and nausea and vomitingâ€"opiate therapy is the primary choice for managing moderate to severe pain. The three most commonly prescribed opiates after gynecologic surgeries are morphine, fentanyl, and hydromorphone. Meperidine, although administered commonly in many obstetric units, is avoided in part because of neurologic side effects associated with its active metabolite, normeperidine. Normeperidine is a cerebral irritant that can cause effects ranging from irritability to seizure.

Morphine

Morphine, the most commonly prescribed opiate following gynecologic surgery, is a potent μ-opiate receptor agonist. Action at this receptor accounts for the analgesia, euphoria, respiratory depression, and decreased gastrointestinal motility seen with morphine. Onset of action is rapid, with the peak effects being seen within 20 minutes of intravenous administration. Its action typically lasts for 3 to 4 hours. Its active metabolite, morphine-6-glucuronide, is excreted renally and thus is well tolerated in low doses in those with liver disease. Pruritus is common following administration, although its genesis is poorly understood. Some investigators theorize that central opiate receptors are stimulated, whereas others speculate a histamine release, as evidenced by urticaria, wheals, and flushing (Bergasa, 1991).

Fentanyl

This potent synthetic opiate is more lipophilic than morphine and displays a shorter duration of action and half life. Peak analgesia occurs within minutes of intravenous administration and lasts for 30 to 60 minutes. Many conscious sedation protocols used during office gynecologic procedures combine fentanyl with a sedative such as midazolam.

Hydromorphone

Hydromorphone, another semisynthetic analogue of morphine, is less lipophilic than fentanyl. It is available for delivery by multiple routes, including oral, intramuscular, intravenous, rectal, and subcutaneous. Hydromorphone achieves its peak analgesia 15 minutes after intravenous administration, and its effect last 3 to 4 hours. Although commonly used during epidural analgesia,

hydromorphone is a suitable patient-controlled analgesia (PCA) alternative in patients with a morphine allergy. Table 39-15 provides a summary of the various pain medications, with equivalent dosages listed.

Table 39-15 Opiod Equivalency Chart/Dosing Data for Opioids

	Approximate Opioid Equianalgesic Dose			Usual Starting Dose			
Drug	**Parenteral (mg)**	**Oral (mg)**	**Duration (h)**	**Adults > 50 kg Body Wt.**		**Children and Adults < 50 kg**	
				Parenteral	**Oral**	**Parenteral**	**Oral**
Morphine IR (Roxanol)	10	30	3â€“4	10 mg	30 mg	0.1 mg/kg	0.3 mg/kg
Morphine SR (Oramorph) (MS contin)	â€”	30	8â€“12	â€”	30 mg	â€”	0.3 mg/kg
Meperdine (Demerol)	75	300	2â€“3	100 mg	NR	0.75 mg/kg	NR
Hydromorphone (Dilaudid)	1.5	7.5	3â€“4	1.5 mg	6 mg	0.015 mg/kg	0.06 mg/kg
Codeine	130	200	3â€“4	60 mg (IM/SC)	60 mg	NR	1 mg/kg
Oxycodone IR (Roxicet)[a] (Percocet)[a]	â€”	30	3â€“4	NA	10 mg	NA	0.2 mg/kg
Oxycodone SR (Oxycontin)	â€”	30	8â€“12	NA	10 mg	NA	0.2 mg/kg
Hydrocodone (Lorcet)[a] (Lortab)[a] (Vicodin)	NA	30	6â€“8	NA	10 mg	NA	0.2 mg/kg
Methadone (Dolophine)	10	20	3â€“4	10 mg	20 mg	0.1 mg/kg	0.2 mg/kg
Fentanyl (Sublimaze) (Duragesic)	0.1	â€”	1	0.1 mg	â€”	â€”	â€”

IM = intramuscular; IR = immediate release; NR = not recommended; SC = subcutaneous; SR = sustained release.

[a] Narcotic-nonnarcotic combination product.

SYSTEM-BASED COMPLICATIONS

Postoperative Urinary Retention

Inability to void with a full bladder is a common problem after gynecologic surgery, and incidences range from 7 to 80 percent depending on the definition used and the surgical procedure (Stanton, 1979; Tammela, 1986). Overdistention can lead to prolonged difficulty with micturition and even permanent detrusor damage (Mayo, 1973). In addition to patient discomfort, recatheterization to treat retention increases the risk of urinary tract infection and may extend hospitalization.

Keita and colleagues (2005) prospectively evaluated risk factors potentially predictive of early postoperative urinary retention. Three major factors were independently associated with an increased riskâ€”age older than 50 years, intraoperative fluid administration greater than 750 mL, and bladder urine volume greater than 270 mL measured on entry to the recovery room. Among gynecologic procedures, the risk is higher after laparotomy compared with laparoscopy (Bodker, 2003).

Despite identifiable risks, all women should be advised of the need for immediate evaluation in the event of absent or difficult voiding. Clinical markers include pain, tachycardia, urge to void without success, and bladder enlargement by palpation or

percussion. These clinical markers have been found to be equivalent to evaluation of urine volume using bedside bladder sonography (Bodker, 2003).

Once retension is identified, catheterization and bladder drainage should follow. Lau and Lam (2004) sought to determine the best catheterization strategy for managing postoperative urinary retention. Compared with overnight bladder decompression with an indwelling catheter, episodic in-and-out catheterization is equally effective. Moreover, infectious morbidity between the two does not differ significantly.

VOIDING TRIALS

Normal urination requires appropriate bladder contractility in the absence of significant urethral resistance (Abrams, 1999). Objective criteria that define "normal function" postoperatively vary and may be assessed using either active or passive voiding trials.

Active Voiding Trial

During this test, the bladder is actively filled with a set volume, and following patient voiding, residual bladder urine volumes are calculated. Initially, the bladder is emptied completely by catheterization. It may be helpful during catheterization for a woman to stand upright to clear the most dependent portions of her bladder. Sterile water infused under gravity then is instilled into the bladder through the same catheter until approximately 300 mL is used or until a subjective maximum capacity is reached. The patient then is given up to 30 minutes to void spontaneously into a urine collection device. The difference between volume infused and volume retrieved is recorded as the *postvoid residual.*

The only published study evaluating the effectiveness of this strategy was reported by Kleeman and colleagues (2002). They evaluated women following surgery for incontinence and prolapse. In their study, a postvoid residual of less than 50 percent carried a recatheterization rate of 8 percent. If patients could void more than 70 percent of the instilled volume spontaneously, there were no failures.

Passive Voiding Trial

As an alternative to active saline instillation, voiding and residuals may be assessed following passive, physiologic filling of the bladder. Initially, the Foley catheter is removed, and a woman is encouraged to drink increased amounts of liquid. She is encouraged to void spontaneously at her first urge to urinate or after 4 hours, whichever is first. Urine volume in a collection device is measured. An in-and-out catheterization or bladder sonogram is then performed to measure the postvoid residual.

An easy rule to remember for evaluating either active or passive voiding trials is the *75/75 rule* â€”spontaneously voiding greater than 75 mL *and* voiding greater than 75 percent of the total volume. This constitutes a successful voiding trial and obviates the need for Foley catheter reinsertion. Alternatively, on the Female Pelvic Medicine and Reconstructive Surgery Service at our institution, a postvoid residual of less than 100 mL constitutes a success.

Pulmonary Complications

Broad definitions hinder our ability to assess the incidence of postoperative pulmonary complications accurately, but reported estimates range from 9 to 69 percent (Calligaro, 1993; Hall, 1991; Qaseem, 2006). Common pulmonary complications encountered by gynecologists are atelectasis and pneumonia. Five significant risk factors for pulmonary complications following abdominal surgery include age older than 60 years, body mass index (BMI) greater than 27, a history of cancer, smoking within the past 8 weeks, and a surgical incision involving the upper abdomen (Brooks-Brunn, 1997).

ATELECTASIS

This condition is characterized by decreased breath sounds or dullness to percussion over affected lung fields. In addition, linear densities in the lower lung fields typify chest radiographic features (Hall, 1991). Classically, atelectasis is associated with low-grade fever. However, Engoren and colleagues (1995) evaluated 100 consecutive adult postoperative patients with radiographically diagnosed atelectasis and found no association between atelectasis and postoperative fever. Despite its common occurrence after abdominal operations, this condition is usually temporary, self-limited, and rarely slows patient recovery or hospital discharge (Platell, 1997). Severe cases of atelectasis can be prevented in many instances using lung expansion therapies described earlier

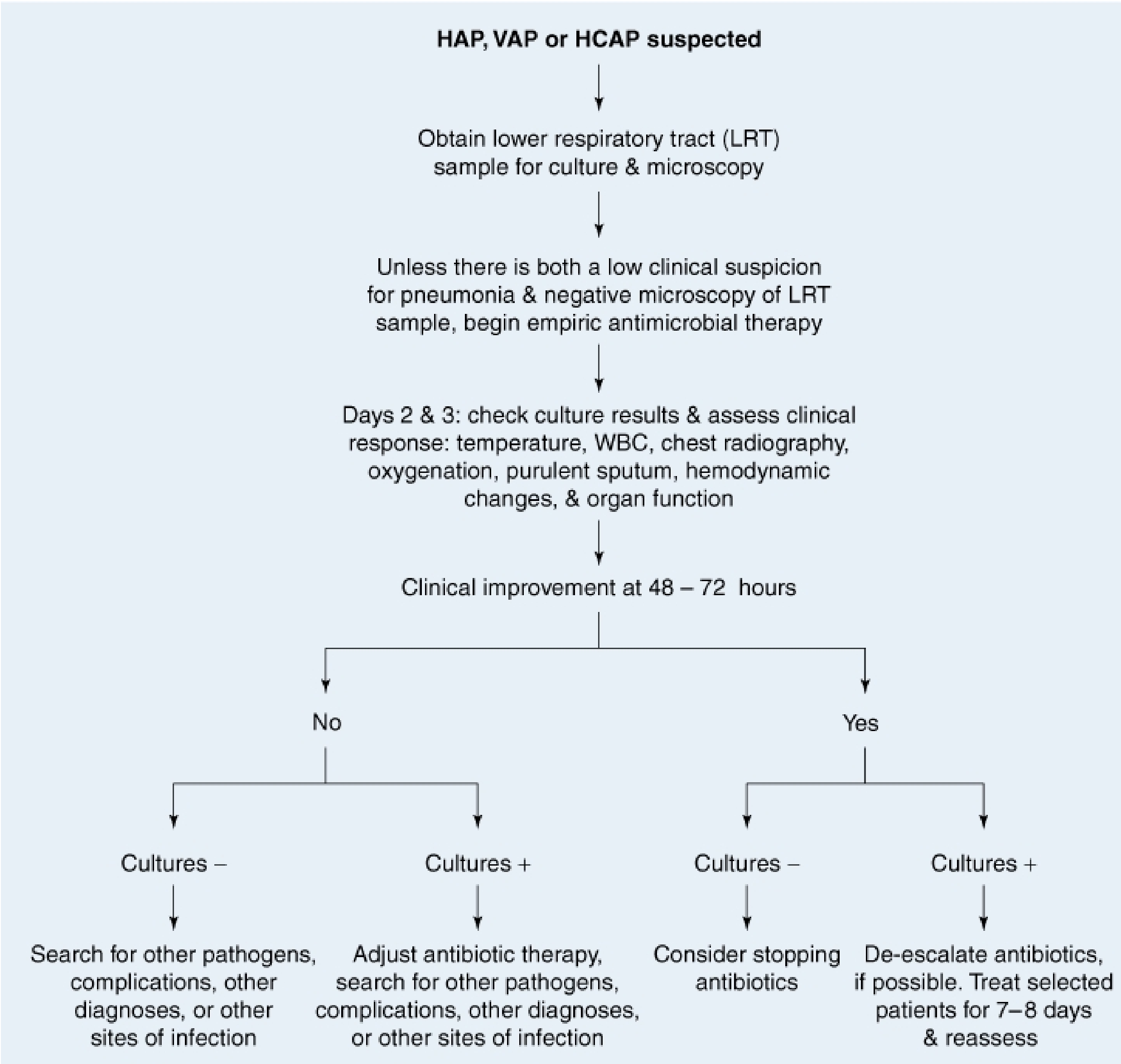
(Lung Expansion Modalities).

HOSPITAL-ACQUIRED PNEUMONIA

This is the second most common nosocomial infection in the United States and carries high associated morbidity and mortality (Tablan, 2004). Its incidence in surgical patients varies and ranges from 1 to 19 percent depending on surgical procedure and hospital surveyed (Kozlow, 2003). Of these infections, bacterial pathogens most typically responsible include aerobic gram-negative bacilli, such as *Pseudomonas aeruginosa* , *Escherichia coli* , *Klebsiella pneumoniae* , and *Acinetobacter* species.

Clinically, pneumonia is diagnosed if chest radiography reveals a new or progressive radiographic infiltrate and if two of three clinical features (i.e., leukocytosis, fever greater than 38Â°C, or purulent secretions) are present. An algorithm supported by the American Thoracic Society is shown in Figure 39-5. As discussed earlier, prevention can be accomplished by using oral endotracheal and orogastric tubes in place of nasal tubes; elevating the head of the bed 30 to 45 degrees, particularly during feeding; and aspiration of subglottic secretions in those unable to clear them (American Thoracic Society, 2005).

FIGURE 39-5



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Algorithm describing management strategies for hospital-acquired pneumonia. HAP = hospital-acquired pneumonia; HCAP = health careâ€"associated pneumonia; VAP = ventilator-associated pneumonia. *(From the American Thoracic Society, 2005, with permission.)*

Gastrointestinal Considerations

RESUMPTION OF BOWEL FUNCTION

Normal gastrointestinal function requires synchronized motility throughout the system, mucosal transport of nutrients, and evacuatory reflexes (Nunley, 2004). However, following intra-abdominal surgery, dysfunction of enteric neural activity typically disrupts normal propulsion. Activity first returns in the stomach and is noted typically within 24 hours. The small intestine also exhibits contractile activity within 24 hours of surgery, but normal function may be delayed for 3 to 4 days (Condon, 1986; Dauchel, 1976). Rhythmic colonic motility resumes last, at approximately 4 days following intra-abdominal surgery (Huge, 2000). Passage of flatus characteristically marks this return of function, and stool passage typically follows in 1 to 2 days.

RESUMPTION OF DIET

Postoperative feeding has been found to be most effective when started immediately postoperatively. Early feeding has been shown to improve wound healing, stimulate gut motility, decrease intestinal stasis, increase splanchnic blood flow, and stimulate reflexes that elicit secretion of gastrointestinal hormones that can shorten postoperative ileus (Anderson, 2003; Braga, 2002; Correia, 2004; Lewis, 2001). The decision to initiation "early feeding" with liquids or with solid food has been studied prospectively (Jeffery, 1996). In patients who were given solid food as the first postoperative meal, the number of calories and protein consumed on the first postoperative day were higher. In addition, the number of patients requiring diet changes to NPO was not statistically different (7.5 percent in the regular diet group and 8.1 percent in the clear diet group). The improved tolerance and better palatability of solids make this a reasonable option.

ILEUS

Postoperative ileus (POI) is a transient impairment of gastrointestinal activity that leads to abdominal distention, hypoactive bowel sounds, nausea and/or vomiting related to gastrointestinal gas and fluid accumulation, and delayed passage of flatus and/or stool (Livingston, 1990).

The genesis of postoperative ileus is multifactorial. First, bowel manipulation during surgery leads to production of factors that contribute to POI: (1) neurogenic factors related to sympathetic overactivity, (2) hormonal factors through the release of hypothalamic corticotropin-releasing factor (CRF), which plays a key role in the stress response, and (3) inflammatory factors (Tache, 2001). Additionally, perioperative opioid use also has a significant role in the etiology of POI. Thus, in selecting these agents, clinicians should balance the beneficial analgesia produced by central opioid receptor binding against the gastrointestinal dysfunction that results from peripheral receptor-binding effects (Holzer, 2004).

No single treatment defines the management of POI. Electrolyte repletion and intravenous fluids to reestablish a euvolemic state constitute traditional therapy. In contrast, routine NGT decompression to promote bowel rest has been challenged by multiple prospective, randomized trials. A recent meta-analysis including nearly 4,200 patients found routine NGT decompression unsuccessful and inferior to its selective use in symptomatic patients. Specifically, patients without NGTs had significantly earlier return of normal bowel function and decreased risks of wound infection and ventral hernia (Nelson, 2005). Additionally, tube-related discomfort, nausea, and hospital stays were reduced. For these reasons, postoperative NGTs are recommended only for symptomatic relief of abdominal bloating and recurrent vomiting (Nunley, 2004).

Gum chewing as a preventative modality for POI has been the focus of several recent studies. Most authors conclude that gum chewing offers no therapeutic value given that there were no significant differences in length of hospitalization or time to first gas or stool passage (Matros, 2006).

SMALL BOWEL OBSTRUCTION

Obstruction of the small intestines may be partial or complete and can result from adhesions following intra-abdominal surgery, infection, or malignancy. Of these, surgical adhesions are the most common cause (Krebs, 1987; Monk, 1994). Small bowel obstruction (SBO) is estimated to develop following 1 to 2 percent of total abdominal hysterectomies, and nearly 75 percent are complete obstructions (Al Sunaidi, 2006). The mean interval between a primary intra-abdominal procedure and SBO is approximately 5 years (Al Took, 1999).

Although the initial management of a SBO is similar to that for postoperative ileus, distinguishing between the two entities is important to prevent serious SBO sequelae. During SBO, the bowel lumen dilates proximal to the obstruction, whereas decompression may develop distally. Bacterial overgrowth in the proximal small bowel may lead to bacterial fermentation and worsening dilation. The bowel wall continues to become edematous and dysfunctional (Wright, 1971). Progressive increases in bowel pressure can compromise perfusion to the intestinal segment and lead to rupture (Megibow, 1991).

Clinical signs that may help to distinguish SBO from POI include tachycardia, oliguria, and fever. Physical examination may reveal abdominal distention, high-pitched bowel sounds, and an empty rectal vault on digital examination. Finally, leukocytosis with a left shift should alert the clinician to possible coexisting bowel ischemia.

For diagnosis, CT scanning is the primary imaging tool to identify SBO. Water-soluble contrast material can help to identify the

cause and severity of an obstruction. Gastrografin, the most commonly used water-soluble dye, is a mixture of diatrizoate meglumine and diatrizoate sodium and aids resolution of small bowel edema because of its high osmotic pressure. Gastrografin (Bracco Diagnostics, Anjou, Quebec) is also theorized to enhance smooth muscle contractility (Assalia, 1994). Although the use of oral Gastrografin does appear to reduce hospital length of stay, it has no therapeutic benefit in adhesion-related SBO (Abbas, 2005).

Nutrition

The primary goals of postoperative nutrition are to improve immune function and promote wound healing while minimizing metabolic disturbances. Despite the additional stress in the immediate postoperative period, underfeeding is accepted for a brief period of time (Seidner, 2006). Table 39-16 offers a summary of the basic metabolic needs in the immediate postoperative period. However, extended protein-calorie restriction in a surgical patient can lead to impaired wound healing, diminished cardiac and pulmonary function, bacterial overgrowth within the gastrointestinal tract, and other complications that increase hospital stays and patient morbidity (Elwyn, 1975; Kinney, 1986; Seidner, 2006). If substantial oral caloric intake is delayed for 7 to 10 days, nutritional support is warranted.

Table 39-16 Postoperative Nutritional Requirements

Nutritional Requirements	**Recommendations**
Basal energy expenditure (BEE) in women	65.5 + 1.9 (height [cm]) + 9.6 (weight [kg]) â€“ 4.7 (age [yr])
Total calories	100% to 120% BEE
Glucose	50â€“70% total caloric intake
	Maintain blood glucose level < 200 mg/dL
Protein	1.5 g/kg/d of current weight (BMI < 25)
	2.0 g/kg/d of ideal weight (BMI > 25)

BMI = body mass index.

Compiled from Nehra, 2002.

ENTERAL VERSUS PARENTERAL NUTRITION

In the absence of contraindications, enteral nutrition is preferred to a parenteral route, especially when infectious complications are compared (Kudsk, 1992; Moore, 1992). Other advantages of enteral nutrition include fewer metabolic disturbances and lower cost (Nehra, 2002).

Hypovolemic Shock

DIAGNOSIS OF HYPOVOLEMIC SHOCK

Circulatory dysfunction causes decreased tissue oxygenation and results in multiorgan failure if not recognized and treated promptly. In gynecology, the most common cause of shock is hemorrhage-related hypovolemia, although cardiogenic, septic, and neurogenic shock should be considered during patient evaluation. Assessment of oxygen perfusion and hemodynamic status is critical in the early postoperative period. Unfortunately, markers such as blood pressure and resting heart rate may be unaffected through early compensation. For example, after an acute blood loss of greater than 25 to 30 percent of total blood volume, hypotension typically lags other markers of multiorgan dysfunction, including oliguria and altered mental status.

In addition to a heightened clinical suspicion of hypovolemia, serum markers may help to provide objective evidence of decreased perfusion and oxygenation. Serum lactate levels have been shown to be more sensitive than blood pressure and cardiac output in predicting severe hemorrhage (Broder, 1964; Dunham, 1991). In addition, serum lactate levels can be used to guide the

effectiveness of resuscitation. Blood gas analysis also can provide a rapid estimate of the serum base deficit. Hemorrhage severity can be predicted accurately using the following stratification: â€“2 to â€“5 (mild hemorrhage), â€“6 to â€“14 (moderate hemorrhage), and â€“15 or less (severe hemorrhage). If patients continue to have dropping base deficits despite aggressive resuscitation, ongoing hemorrhage should be assumed (Davis, 1988). Of note, immediate hematocrit levels do not predict the severity of acute blood loss as accurately as serial trends.

TREATMENT OF HYPOVOLEMIC SHOCK

Treatment of hypovolemic shock centers on control of ongoing hemorrhage and restoration of intravascular volume. One easy mnemonic used to describe treatment is *ORDER* , which represents *o* xygenate, *r* estore, *d* rug therapy, *e* valuate, and *r* emedy (American College of Obstetricians and Gynecologists, 1997). Initially, supplemental oxygen is provided to avoid tissue desaturation (Wilson, 2003). Simultaneously, a rapid infusion of isotonic crystalloid solutions through two large-bore intravenous lines can quickly replace volume. In the face of refractory hypotension, supplemental colloids and red blood cell transfusion may be necessary (see Chap. 40, Fluid Resuscitation and Blood Transfusion). In the presence of hypovolemia, vasopressors generally are not recommended except to temporarily assist with an unstable condition while fluid resuscitation is administered. During treatment, resuscitation efforts are monitored continuously through central venous pressures, urine output, and the patient's general status. Finally, if ongoing bleeding is suspected, the benefits of operative intervention may outweigh the risks of continued conservative therapy. Intraoperatively, isolation and control of hemorrhage should be approached systematically (see Chap. 40, Steps of Hemorrhage Management).

After the patient is stabilized, close surveillance for electrolyte abnormalities, coagulation imbalance, and ischemic organ injury is essential.

Postoperative Fever Evaluation

One of the most common problems encountered postoperatively is fever. Although fever may reflect an infectious process, most are self-limited (Garibaldi, 1985). However, for those with persistent symptoms, a systematic approach to patient evaluation will help to differentiate inflammatory from infectious etiologies.

PATHOPHYSIOLOGY OF THE FEBRILE RESPONSE

Fever is a response to inflammatory mediators, termed *pyrogens* , that originate either endogenously or exogenously. Circulating pyrogens lead to the production of prostaglandins (primarily PGE_2), which elevate the thermoregulatory set point. The inflammatory cascade produces a number of cytokines (interleukin-1, interleukin-6, tumor necrosis factor α) found in the circulation after a variety of eventsâ€”surgery, cancer, trauma, and infection (Wortel, 1993). Thus, a differential diagnosis of a postoperative fever should include noninfectious and infectious causes.

ETIOLOGY

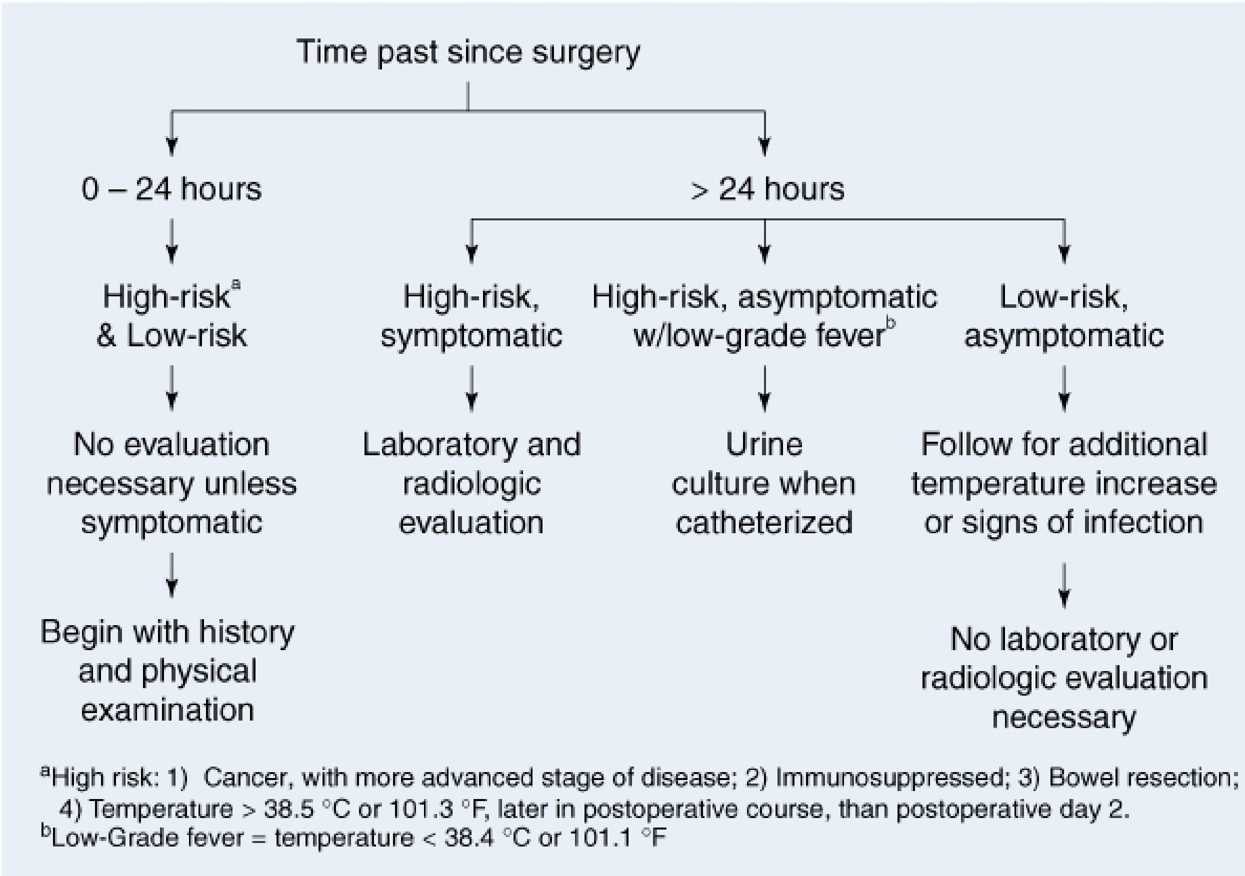
Postoperative fevers that develop more than 2 days following surgery are more likely to be infectious. The most common causes may be broadly categorized and are reflected in the mnemonic, the *five W's.* These represent wind, water, walking, wound, and wonder drug. First, pneumonia should be considered, and women at greatest risk are those who have been mechanically ventilated for a prolonged period, have an NGT in place, or have pre-existing COPD. Additionally, catheterization places women at risk for developing a urinary tract infection. Logically, duration of catheterization correlates positively with the risk for this infection. Venous thromboembolic disease may present with low-grade fever, and patients with VTEs commonly present with other disease-specific symptoms. For example, women with DVT often complain of unilateral lower extremity edema and erythema. Those with PTE may note dyspnea, cough with blood-tinged sputum, chest pain, tachycardia, and symptoms of hypotension (Stein, 2000). Fever related to surgical site infections usually develops 5 to 7 days after surgery. These infections may involve the pelvis or abdominal wall layers, and their management is discussed later in this chapter and in Chapter 3, Pain. Finally, medications commonly used postoperativelyâ€”such as heparin, beta-lactam antibiotics, and sulfonamide antibioticsâ€”may cause a rash, eosinophilia, or drug fever.

CLINICAL EVALUATION

Evaluations that rotely include CBC, urinalysis, blood cultures, and chest radiographs have been evaluated in multiple studies and

are inefficient and ineffective (Badillo, 2002; de la Torre, 2003; Schey, 2005). Thus, initial assessment of a woman with postoperative fever should be individualized and begin with a focused history and physical examination. The simple diagnostic algorithm presented in Figure 39-6 can be used as one high-yield, cost-effective strategy for the management of a woman with postoperative fever.

FIGURE 39-6



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Algorithm for evaluation of postoperative fever. *(From de la Torre, 2003, with permission.)*

Wound Dehiscence

Despite the clinical advances made in the arenas of anesthesia, preoperative antibiotics, suture technology, and postoperative care, the incidence of wound disruptions remains largely unchanged (Cliby, 2002). Dehiscence prolongs hospital stay and requires labor-intensive care. Thus, a surgeon should have knowledge of modifiable risk factors and treatment options for these complications.

CLASSIFICATION AND INCIDENCE

The level to which a wound may open varies and may involve the subcutaneous and skin layers. More seriously, separation also may include abdominal wall fascia. Superficial separations often follow a wound infection originating from a hematoma or seroma and have a reported incidence of between 3 and 15 percent (Owen, 1994; Taylor, 1998). Fascial dehiscences, on the other hand, occur less frequently and are fatal in nearly 25 percent of cases (Carlson, 1997). Fascial necrosis from sutures held under too much tension leads to failure of sutures to remain anchored in the fascia (Bartlett, 1985). These layers then may separate with only minimal increases in intra-abdominal pressure.

Wound classification greatly predicts the subsequent risk of developing a postoperative wound infection (Cliby, 2002). For those with clean wounds, the risk of infection is less than 5 percent; those with clean contaminated wounds, 2 to 10 percent; those with contaminated wounds, 15 to 20 percent; and those with dirty wounds, more than 30 percent. Descriptive criteria for these wound categories are found in Table 3-30.

PREVENTION

In addition to wound type, other important risk factors for developing a wound dehiscence include general patient health, proper surgical technique, and appropriate timing of preoperative antibiotics.

General Patient Health

Riou and colleagues (1992) found that age greater than 65 years, pulmonary disease, malnutrition, obesity, malignancy, and hypertension contribute to a patient's risk of developing subsequent wound disruption. Diabetes mellitus and smoking are two other contributors to surgical site infections that lend themselves to preoperative optimization (Cheadle, 2006). Although many of these are not modifiable, the presence of these risks should prompt increased surveillance postoperatively.

Proper Surgical Technique

In the operating room, a surgeon has multiple opportunities to modify risks associated with wound disruption. Proper surgical technique maintains hemostasis, handles tissues gently, removes devitalized tissue, closes dead spaces, encourages use of monofilament suture, includes indicated placement of closed suction drains, and sustains normothermia (Mangram, 1999). For example, Kurz and co-workers (1996) demonstrated that maintaining normothermia in patients undergoing abdominal surgery significantly reduced postoperative wound infection rates from 19 to 6 percent.

Use of electrosurgery instead of scalpel for abdominal entry is common and offers speed, hemostasis, comparable wound healing, and decreased requirements for postoperative analgesia (see Chap. 40, Electrosurgery) (Chrysos, 2005). The cutting properties of electrosurgery cause cells to explode by conversion of cell water to steam. This method of heat dissipation leads to minimal lateral thermal tissue damage. Coagulation mode, on the other hand, achieves hemostasis through formation of a superficial eschar and desiccation (the fibrous binding between dehydrated, denatured cells of vessel endothelium). Therefore, tissue dissection should be performed using a cutting mode, whereas hemostasis is best achieved with directed coagulation. In addition, less tissue damage and fewer tracts for bacterial overgrowth result from minimizing the number of surgical strokes during incision.

Dead space closure using a subcutaneous suture in Camper fascia at the time of cesarean delivery has been shown to reduce superficial wound disruptions significantly in those with at least 2-cm subcutaneous depth (Naumann, 1995). Well-designed prospective studies in gynecologic populations are lacking. Skin closure using subcuticular suturing has lower wound separation rates than staples (Johnson, 2006).

DIAGNOSIS

Superficial wound separations usually present 3 to 5 days after surgery, with wound erythema and new-onset drainage. Once identified, an isolated wound cellulitis often can be treated with systemic antibiotics. However, a delay in evacuating infected inflammatory exudates from the subcutaneous layer dead space can weaken fascia and increase the risk of fascial dehiscence.

Fascial dehiscences generally present within the first 10 days postoperatively. Superficial disruption of the subcutaneous layer and extensive leakage of peritoneal fluid/purulent drainage are indicative. Given the high mortality risk associated with fascial dehiscence and bowel evisceration, examination under anesthesia to estimate the extent of separation is warranted.

TREATMENT OF SUPERFICIAL WOUND DEHISCENCE

The focus of wound management should be to expedite healing while minimizing complications and costs.

Wet-to-Dry Dressing Changes

The initial focus of wound management is evacuation of all hematomas and/or seromas and treatment of underlying infection. Modern wound care has revised some of the classic axioms behind healing through secondary intention.

Irrigation used for wound dressings should remove surface bacteria without disrupting normal healing components. Povidone-

iodine, iodophor gauze, dilute hydrogen peroxide, and Daiken solution are cytotoxic to white blood cells and should not be used in wound care (Bennett, 2001; O'Toole, 1996).

Ideally, wound dressings are removed daily and replaced with properly hydrated materials. In very necrotic wounds, allowing gauze to dry and pulling tissue adherent to the gauze with each change is acceptable. More frequent changes should be avoided because they lead to aggressive dÃ©bridement of vital tissues and slow wound healing. Table 39-17 lists products used in modern wound care.

Table 39-17 Wound Care Products

Product	Description
Antifungal cream	Topical cream used as treatment for superficial fungal infections of the periwound skin; contains 2% miconazole nitrate.
Calcium alginate	Calcium alginate is a solid that exchanges calcium ions for sodium ions when it contacts any substance containing sodium such as wound fluid. The resulting sodium alginate is a gel that is nonadhesive, nonocclusive, and conformable to wound bed. Indicated for moderately or highly draining wounds.
Enzymatic dÃ©brider	Topical solution that breaks down necrotic tissue by directly digesting the components of slough or by dissolving the collagen that holds necrotic tissue to the underlying wound bed.
Film	Thin, transparent polyurethane sheets coated on one side with acrylic, hypoallergenic adhesive. The adhesive will not stick to moist surfaces, and the film is impermeable to fluids and bacteria, but semipermeable to oxygen and water vapor. Indicated in superficial wounds with little or no exudate.
Foam	Polyurethane sheets containing open cells capable of holding fluids and pulling them away from the wound bed. Foams provide absorbency while keeping the wound moist. Indicated in moderately or highly draining wounds.
Gauze	Woven or nonwoven cotton or synthetic blends.
Hydrogel	Formulated in sheets or gels. Glycerin-, saline-, or water-based to hydrate the wound. Indicated in dry or minimally draining wounds.
Silver nitrate	Used to treat overgrown granulation tissue. Apply stick to hypergranulation tissue.

From Sarsam, 2005, with permission.

Negative-Pressure Wound Therapy

This therapy generates subatmospheric pressure by a wound vacuum device that is applied either continuously or intermittently to an open subcutaneous wound. The negative pressure generated by such devices offers three benefits to wound care: (1) evacuates wound drainage to reduce bacterial colonization, (2) promotes release of cytokines that are helpful in wound healing, and (3) increases blood flow and oxygenation to tissues to uniformly reduce wound size and improve angioneogenesis (Fabian, 2000; Morykwas, 1997).

Delayed Primary Closure

Approximately 4 days after wound disruption and resolution of subcutaneous infection, a superficial vertical mattress suture closure may be used to reapproximate subcutaneous and skin tissue edges (Wechter, 2005). Overall, this strategy reduces healing time by 5 to 8 weeks and significantly decreases the number of postoperative visits. Bedside closure is typically well tolerated using local anesthesia and 2-0 polypropylene suture. Alternatively, wounds may be allowed to close by secondary intention.

TREATMENT OF FASCIAL DEHISCENCE

Early recognition of abdominal wall separation is critical in reducing serious morbidity and mortality associated with fascial

dehiscence. This is regarded as a surgical emergency, and a gynecologist must first determine if a fascial dehiscence is associated with evisceration of abdominal contents. If discharge of abdominal contents is noted, an abdominal binder with sterile towels soaked in saline can be use to replace abdominal contents and temporize the situation. Broad-spectrum antibiotics generally are recommended to minimize ensuing peritonitis.

The final goal of treatment is closure. For critically ill patients with significant edema, temporarily maintaining anterior abdominal wall integrity until a patient is stable enough to tolerate a definitive operative closure is reasonable. Fascial closure under general anesthesia is performed after sufficient dÃ©bridement of necrotic or infected tissue. An interrupted mass closure using a no. 2 permanent suture typically is recommended. However, if primary closure is under significant tension, a synthetic mesh bridge may be required. If the subcutaneous wound is left open, wet-to-dry dressing changes may be performed until the decision has been made to proceed with a delayed primary closure or allow secondary intention to compete the process (Cliby, 2002).

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INTRAOPERATIVE CONSIDERATIONS: INTRODUCTION

Although conservative medical management of most gynecologic conditions is preferred, many conditions are not amenable to this approach, and surgery is required. Successful gynecologic surgery is directed at treatment of underlying pathology and uses techniques that maximize tissue healing and patient recovery. During any procedure, intraoperative complications may be encountered, and surgeons should be familiar with these challenges and their management.

ANESTHESIA SELECTION

Many anesthetic options are available for patients undergoing gynecologic procedures. Paracervical blockade using local anesthetic agents may be used alone or more commonly, with conscious sedation prior to dilatation and curettage or hysteroscopy. However, in patients requiring a greater degree of anesthesia, general anesthesia or regional epidural or spinal techniques typically are used.

The delivery of these anesthetic techniques should be provided by clinicians who are skilled with their placement and are capable of managing their side effects. Thus, in general, paracervical blockade and intravenous sedation may be provided by gynecologists. General, epidural, and spinal anesthesia typically are delivered and managed by anesthesiology staff.

The selection of anesthesia for gynecologic surgery is complex. Clinical factors such as the procedure planned, extent of disease, and patient comorbidities weigh heavily in the decision process. Moreover, personal preferences of the patient, anesthesiologist, and surgeon influence choice. Lastly, the providing hospital or clinic may further define options based on their practicing norms and availability of personnel or equipment. For example, an outpatient gynecology clinic may have supporting personnel and equipment sufficient for paracervical blockade or intravenous conscious sedation but may lack sophisticated equipment or expertise required for regional or general anesthesia.

In all cases, both the anesthesia provider and the surgeon should be prepared for potential problems. Cases using paracervical blockade may be complicated by inadequate levels of anesthesia or conversely, by anesthetic toxicity. Conscious sedation also may fail to provide adequate analgesia or alternatively, may lead to respiratory depression. Difficult patient intubation may complicate general anesthesia, and regional anesthetic procedures may lead to higher than anticipated levels of blockade and respiratory muscle dysfunction. Thus, no procedure is free of potential risk, and contingency plans for each should be in place.

Paracervical Block

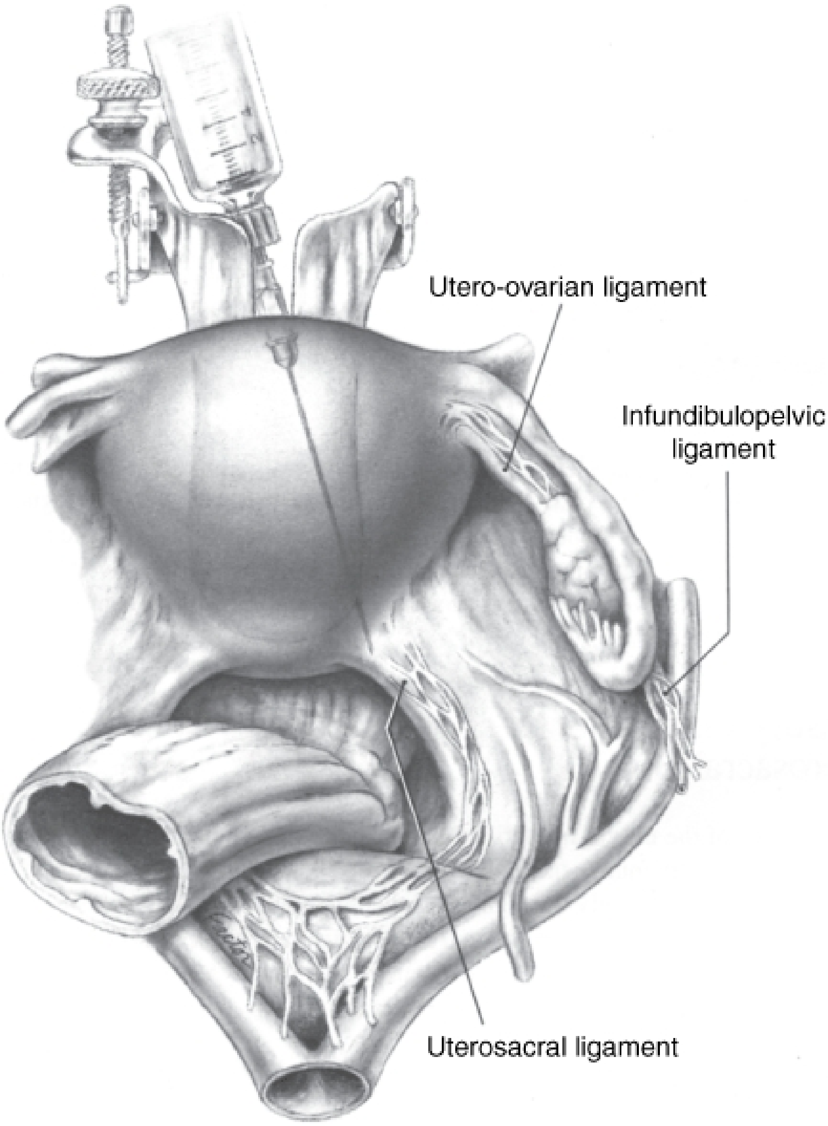
ANATOMY

The cervix, vagina, and uterus are richly supplied by nerves of the uterovaginal plexus. (see Fig. 38-23B). Also known as *FrankenhÃ¤user plexus,* this plexus lies within the connective tissue lateral to the uterosacral ligaments. For this reason, paracervical injections are most effective if placed immediately lateral to the insertion of the uterosacral ligaments into the uterus (Rogers, 1998).

TECHNIQUE

Injection of divided doses may be given at 4 and 8 o'clock at the cervical base (Figs. 40-1 and 40-2). Alternatively, injections may be placed at 3, 6, 9, and 12 o'clock sites. However, this increased number of sites appears not to improve analgesic effects (Glantz, 2001).

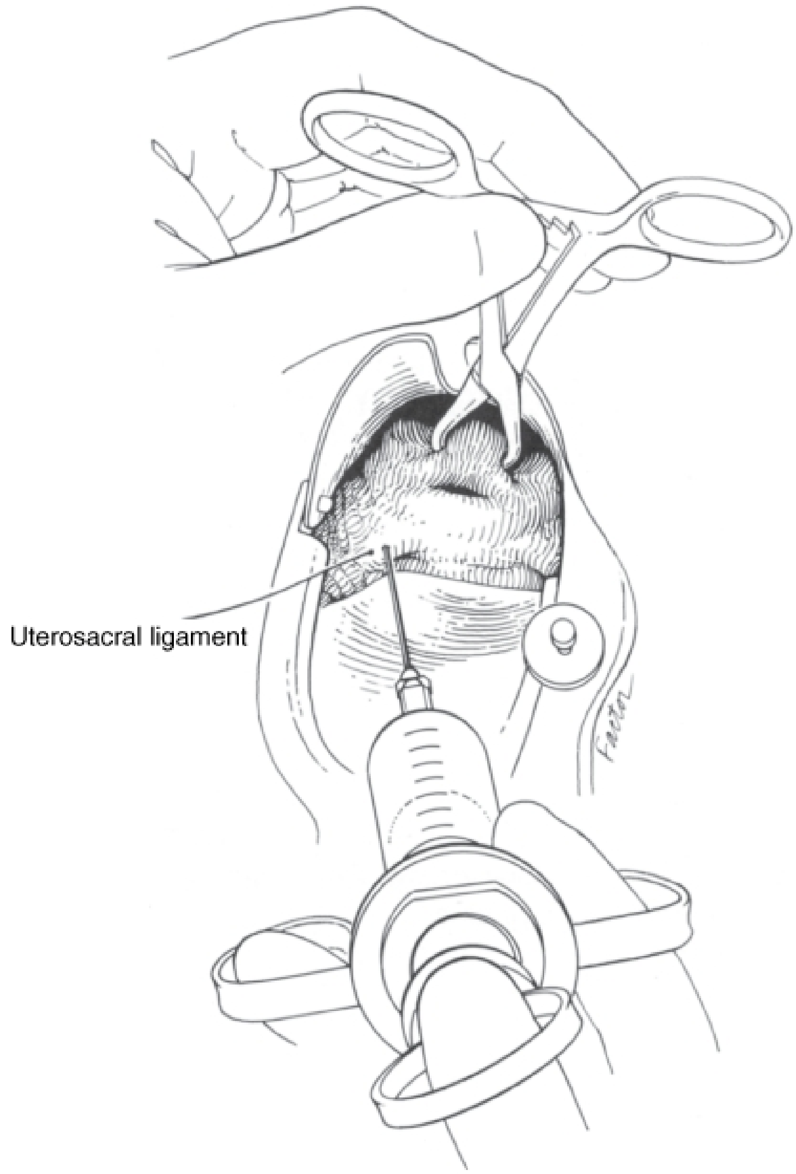
FIGURE 40-1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Abdominal view of a paracervical block. Local anesthetics are infiltrated near sensory innervation of the cervix, which lies lateral to the uterosacral ligament. *(From Penfield, 1986, with permission.)*

FIGURE 40-2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Vaginal approach to the injection of local anesthetics into cervical base at 4 and 8 o'clock. *(From Penfield, 1986, with permission.)*

In most cases, total doses of 10 mL of 0.25-percent bupivacaine, 1-percent mepivicaine, or 1- or 2-percent lidocaine may be administered (Table 40-1) (Cicinelli, 1998; Hong, 2006; Lau, 1999). However, specific calculation of a maximum safe dose for each patient before injection is recommended (Dorian, 2005). The toxic dose of lidocaine approximates 4.5 mg/kg. Thus, for a 50-kg woman: 4.5 mg/kg $\times$ 50 kg = 225 mg.

Table 40-1 Characteristics of Local Anesthetics				
Drug	**Available Concentrations, %**	**Maximum, mg/kg**	**Maximum Dose with Epinephrine Combined, mg/kg**	**Duration, h**
Moderate-duration				
Lidocaine	0.5, 1, 2	4.5	7	0.5â€“1
Mepivicaine	0.5, 1	4	7	0.75â€“1.5
Prilocaine	0.5, 1	7	8.5	0.5â€“1.5
Long-duration				
Bupivicaine	0.25, 0.5	2.5	3	2â€“4
Etidocaine	0.5, 1	4	5.5	2â€“3

For any drug solution, 1-percent = 10 mg/mL. Thus, if a 1-percent lidocaine solution is used for a 50-kg woman, the calculated allowed amount would be: 225 mg Ã· 10 mg/mL = 22.5 mL.

Anesthesia is presumed to result from pharmacologic nerve conduction blockade by a local anesthetic agent (Chanrachakul, 2001). Each drug has a different recovery time based on individual solubility and tissue binding. Moreover, addition of epinephrine to these solutions leads to local vasoconstriction, which enhances the quality of analgesia, prolongs the duration of action, and decreases toxicity. Return of neural function is spontaneous as the drug is metabolized.

Alternatively, injection itself may have an immediate anesthetic effect by swelling surrounding tissue and exerting mechanical pressure on nerves to disrupt neural transmission. In support of this, similar pain scores were noted in women undergoing elective abortion whether a procedure began immediately after paracervical injection or following a several-minute delay to allow pharmacologic blockade (Phair, 2002; Wiebe, 1995).

USAGE

Paracervical block is used most commonly during first-trimester pregnancy evacuation but also has been used prior to cervical ablative or excisional procedures, transvaginal sonographically guided oocyte retrieval, and in-office hysteroscopy.

Often, paracervical block is combined with nonsteroidal anti-inflammatory drugs (NSAIDs) or intravenous conscious sedation or both. Conscious sedation may be achieved with several agents, but intravenous midazolam combined with fentanyl is used frequently (Lichtenberg, 2001). Table 10-2 lists therapeutics doses of NSAIDs.

Table 40-2 The Lumbosacral Plexus Nerve Plexus (L1-S4)			
Nerve	**Origin**	**Motor Function**	**Sensory Function**
Ilioinguinal	L1	None	Inferior abdominal wall, mons pubis, labia majora
Iliohypogastric	L1	None	Inferior abdominal wall, upper lateral gluteal region
Genitofemoral	L1-2	None	Labia majora, anterior superior thigh
Lateral femoral	L2-3	None	Anterolateral thigh
Cutaneous femoral	L2-4	Hip flexion, adduction; Knee extension	Anterior and medial thigh, medial calf
Obturator	L2-4	Thigh adduction, lateral rotation	Superomedial thigh
Pudendal	S2-4	Muscles of perineum; External anal and urethral sphincters	Perineum
Sciatic	L4-S3		
Common peroneal	L4-S2	Knee flexion; Foot dorsiflexion, eversion; Toe extension	Lateral calf, foot dorsum
Tibial	L4-S3	Thigh extension; Knee flexion; Foot plantar flexion; inversion	Foot plantar surface, toes

TOXICITY

Increased doses of local anesthetics may lead to clinically significant conduction blockade within the central nervous system (CNS) and heart. Signs range from drowsiness, tinnitus, perioral tingling, and visual disturbances to confusion, seizure, coma, and ventricular arrhythmia. In monitoring patients, surveillance for the subtle symptoms of CNS toxicity is important because the therapeutic-to-toxic ratios are often narrow with these agents.

When toxicity develops, cardiac effects are potentiated by acidosis, hypercapnia, and hypoxia. Thus, treatment of toxicity typically includes intravenous access, adequate oxygenation, and seizure control. A benzodiazepine such as diazepam given intravenously is effective anticonvulsant therapy (Naguib, 1998). For treatment, diazepam, 2 mg/min, is administered until seizures stop or a total dose of 20 mg is delivered.

Intrauterine Instillation

Injection of local anesthetic solutions through a catheter into the uterine cavity has been reported to lower pain scores in women undergoing in-office hysteroscopy or endometrial biopsy (Cicinelli, 1997; Trolice, 2000). The presumed mechanism is anesthetic blockade of nerve endings within the endometrial mucosa. Studies have used 5-mL doses of 2-percent lidocaine or of 2-percent mepivicaine. Edleman and co-workers (2004, 2006) combined instillation of 5 mL of 4-percent lidocaine with paracervical blockade for first-trimester abortion procedures. However, a significant number of women reported symptoms attributed to lidocaine toxicity, including numbness, tingling, and ear ringing.

PATIENT POSITIONING

Anesthetized patients who undergo prolonged gynecologic procedures are at risk for development of peripheral neuropathy of their upper or lower extremities. These neuropathies are uncommon, and cited incidences approximate 2 percent of gynecologic cases

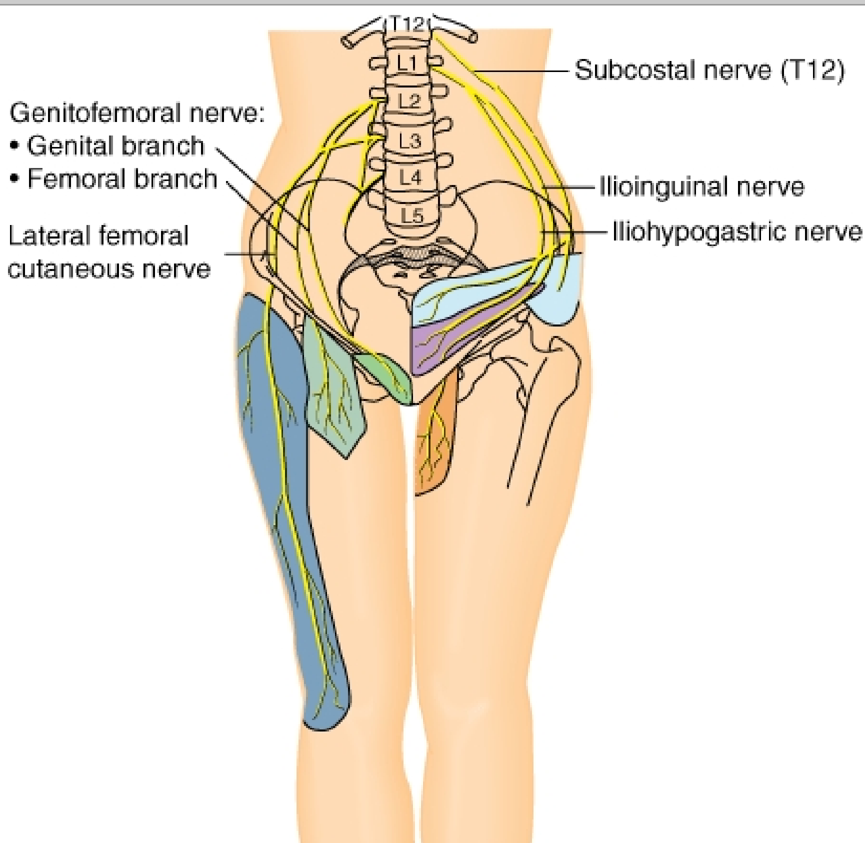
(Cardosi, 2002). Neurologic deficits typically are mild, transient, and resolve spontaneously. However, infrequently, prolonged or permanent disability may result.

During gynecologic surgery, lower extremity injuries may involve nerves of the lumbosacral plexus (Table 40-2). In most cases, peripheral neuropathy follows improper placement of self-retaining retractors, radical pelvic dissection, or improper patient positioning, especially in the lithotomy position. Mechanisms of injury include surgical nerve transection, rupture following increased stretch, or nerve ischemia. Ischemia may result from compression of perineural vessels during prolonged or pronounced nerve stretch or compression.

Although any patient may develop postoperative neuropathy, higher rates have been noted in patients who smoke, who have anatomic abnormalities, or who are thin, diabetic, or alcoholic. Use of self-retaining retractors and prolonged surgical duration are additional risks (Warner, 1994).

Symptoms reflect functional loss of the affected nerve. Motor loss typically manifests as muscle weakness, whereas sensory loss may be noted as anesthesia, paresthesia, or pain in the nerve's sensory distribution (Fig. 40-3). Therefore, a detailed neurologic examination allows clinical identification of most peripheral neuropathies. Electrodiagnostic testing is indicated if motor function is diminished, but this lacks adequate sensitivity in cases of sensory loss (Knockaert, 1996). Generally, electromyography is most useful after a 2- to 3-week delay to permit denervational changes to fully develop within the affected muscles (Winfree, 2005).

FIGURE 40-3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Peripheral nerves and their corresponding areas of sensory innervation. *(From Ducic, 2006, with permission.)*

Treatment will vary depending on whether motor or sensory function is affected. If motor function is impaired, neurologic consultation is warranted. Physical therapy should begin immediately to minimize contracture and muscle atrophy. Alternatively, for those with only mild sensory losses, observation for return of function is reasonable. For those with pain, treatments may include serial trigger point injection with local anesthetics; oral analgesics; biofeedback; and gabapentin. If conservative options fail to bring sufficient relief, neurectomy ultimately may be required for those with chronic pain (Madura, 2005).

Laparotomy

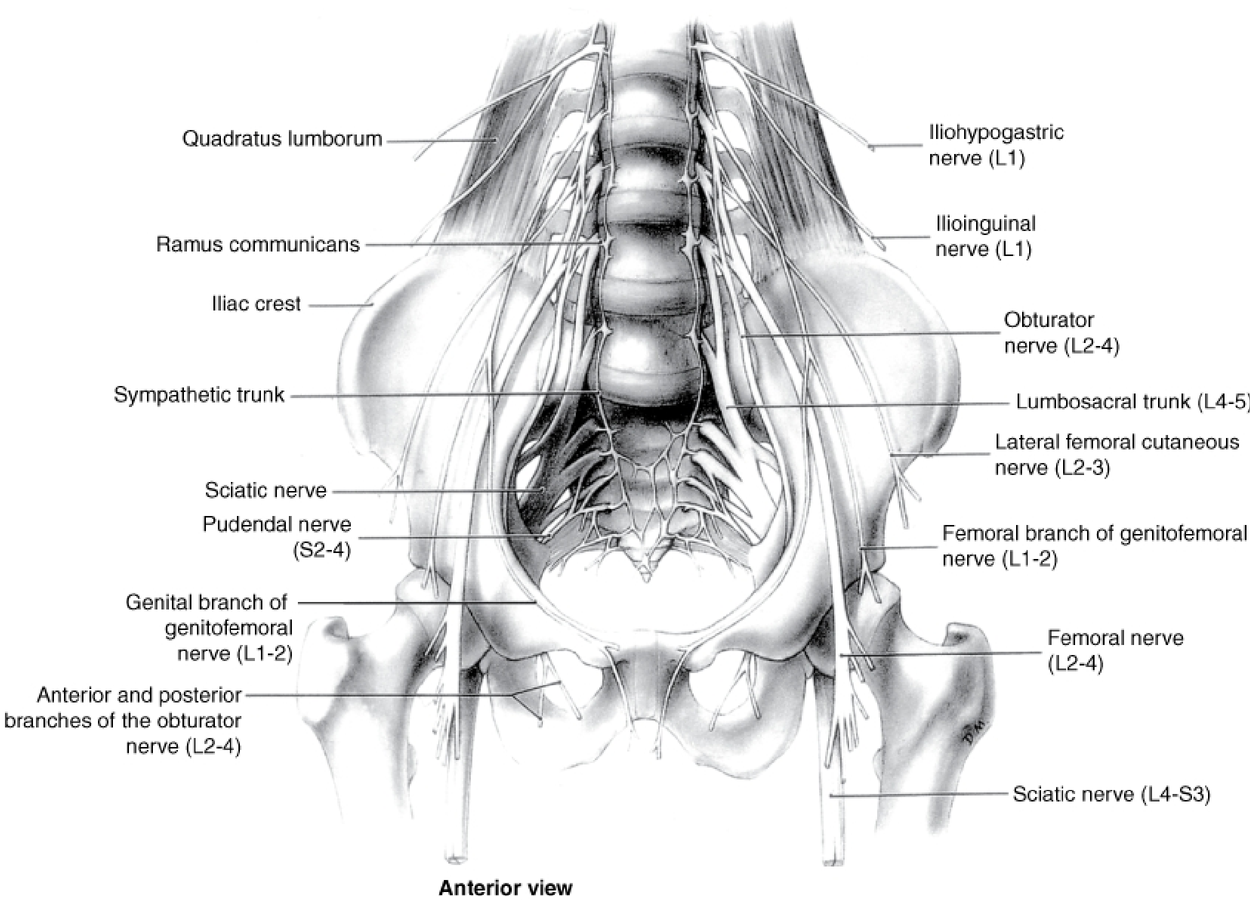
Nerve injury may occur at the time of laparotomy and more commonly results from poor retractor placement, wide transverse abdominal wall incisions, and extensive dissections at the pelvic sidewall.

SELF-RETAINING RETRACTORS

Femoral Nerve Injury

The femoral nerve perforates the psoas muscle early in its course to provide motor function to the iliac, sartorius, and quadriceps muscles and sensory function to the anteromedial thigh and medial leg (Fig. 40-4). Before exiting the pelvis, this nerve passes medially beneath the inguinal ligament to enter the femoral triangle lateral to the femoral artery and vein. This nerve can be compressed anywhere along its course but is particularly susceptible within the body of the psoas muscle and at the inguinal ligament.

FIGURE 40-4

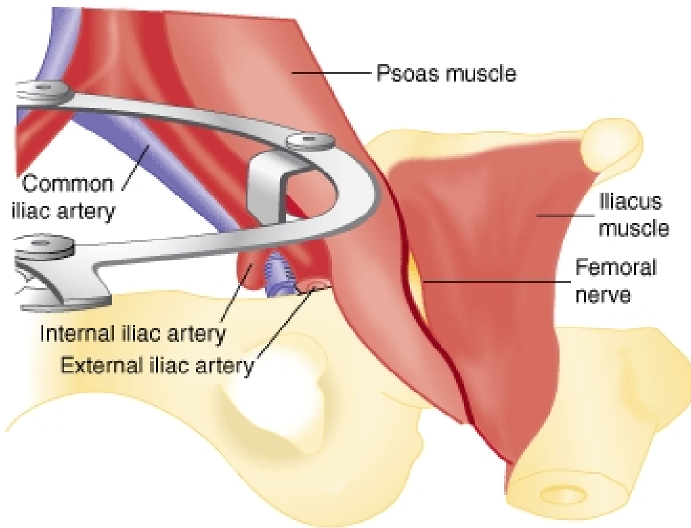


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Nerves of the lumbosacral nerve plexus. *(From Irvin, 2004, with permission.)*

Improper placement of a self-retaining retractor is the most common cause of surgical femoral nerve injury, and rates following abdominal hysterectomy may reach 10 percent (Goldman, 1985; Kvist-Poulsen, 1982). Injury results from compression of the psoas muscle and femoral nerve by retractor blades, and increasing blade size has been implicated with increasing rates of injury (Fig. 40-5) (Kvist-Poulsen, 1982).

FIGURE 40-5



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Lateral blade of a self-retaining retractor can compress the psoas major muscle and femoral nerve against the pelvic sidewall. *(From Irvin, 2004, with permission.)*

Women with femoral neuropathy may display impaired motor function with weakness or inability to flex the hip or extend the knee. The patellar reflex is usually absent. Impaired sensory function is characterized by paresthesia over the anteromedial thigh and medial calf.

In prevention, lateral retractor blades should be selected and positioned such that only the rectus abdominis muscle and not the psoas muscle is retracted (Chen, 1995). For thin patients, folded laparotomy sponges may be placed between the retractor rim and skin to elevate blades away from the psoas muscle.

Genitofemoral Nerve Injury

The genitofemoral nerve pierces the medial border of the psoas muscle and traverses below the peritoneum on this muscle's surface. Above the inguinal ligament, it divides into genital and femoral branches. The femoral branch follows the external iliac artery, continues behind the inguinal ligament, and exits through the fascia lata to provide sensory function to the femoral triangle. The genital branch enters the inguinal canal to supply sensation to the labia majora and mons pubis. Similar to the femoral nerve, the genitofemoral nerve may suffer injury with compression of the psoas muscle, and sensory symptoms follow the distribution of the nerve (see Fig. 40-3) (Murovic, 2003). In addition, this nerve may be injured during removal of a large pelvic mass adherent to the sidewall or during external iliac lymph node dissection (Irvin, 2004).

Lateral Femoral Cutaneous Nerve Injury

This nerve appears at the lateral border of the psoas major muscle just above the crest of the ilium. It courses obliquely across the anterior surface of the iliac muscle and dips beneath the inguinal ligament laterally as the nerve exits the pelvis. The lateral

femoral cutaneous nerve may be compressed as the nerve courses along the pelvic wall (Aszmann, 1997). Sensory symptoms extend over the anterolateral hip and thigh. Painful neuropathy specifically involving the lateral femoral cutaneous nerve carries the specific name *meralgia paresthetica* .

TRANSVERSE INCISIONS

Nerve injury during transverse abdominal entry is common. It typically involves the ilioinguinal and iliohypogastric nerves or less frequently, branches of the genitofemoral nerve. The ilioinguinal and iliohypogastric nerves emerge through the internal oblique muscle approximately 2 to 3 cm inferomedial to the anterosuperior iliac spine (Whiteside, 2003). The iliohypogastric nerve extends a lateral branch to innervate the lateral gluteal skin. An anterior branch reaches horizontally toward the midline and runs deep to the external oblique muscle. Near the midline, this nerve perforates the external oblique muscle and becomes cutaneous to innervate the superficial tissues and skin in the region above the symphysis pubis (see Fig. 38-4). The ilioinguinal nerve extends medially to enter the inguinal canal and innervates the lower abdomen, labia majora, and upper thigh.

These are sensory nerves, and fortunately, most skin anesthesia or paresthesias that follow their injury resolves with time. For this reason, injuries frequently are underreported by both patients and clinicians.

Pain, however, in some cases may result and may begin immediately following surgery or many years later. It is usually sharp and episodic and radiates to the upper thigh, labia, or upper gluteal region. Later, sensations may become chronic and burning (Ducic, 2006).

Diagnosis can be confirmed with trigger point injection of local anesthetics. Sippo and colleagues (1987) describe injection of a solution containing a 2:1 ratio of 0.5-percent bupivacaine and 1-percent lidocaine. The needle is inserted at a point 1 cm inferomedial to the anterosuperior iliac spine to reach the depth of the external oblique muscle. Solution is injected medially in a fan-shaped distribution. Pain relief following nerve blockade is diagnostic.

PELVIC SIDEWALL DISSECTION

Lymph node dissection, tumor excision, or endometriosis resection performed at the pelvic sidewall may injure the obturator or genitofemoral nerves. Moreover, the obturator nerve also can be injured during dissection within the space of Retzius during urogynecologic procedures (see Fig. 38-25).

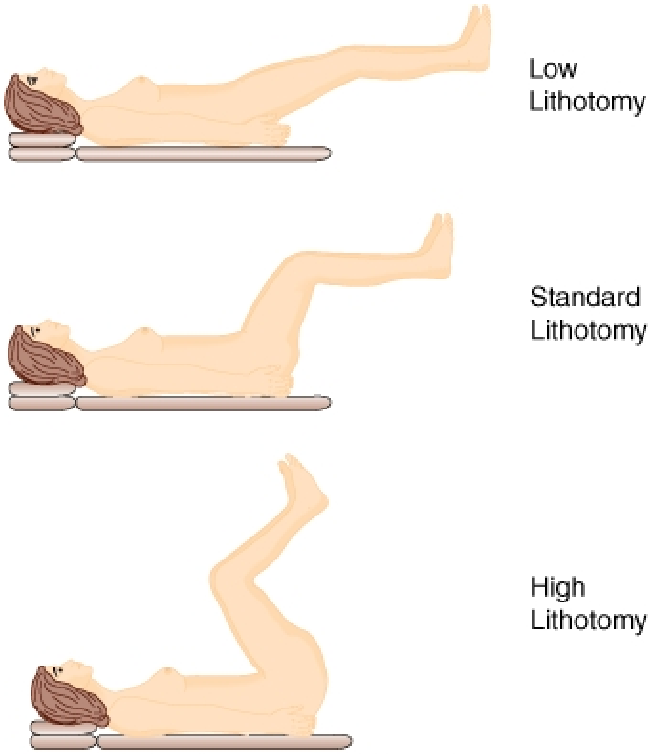
Obturator Nerve Injury

This nerve pierces the medial border of the psoas muscle and extends anteriorly along the lesser wall of the pelvis. The obturator nerve exits through the obturator foramen to supply adductor muscles of the thigh and the obturator externus muscle, which rotates the thigh laterally. Sensory innervation covers the superomedial thigh. Women with obturator neuropathy display weakness of hip adduction and external rotation and sensory symptoms extending over the medial thigh (Vasilev, 1994).

Dorsal Lithotomy

This surgical position is used for vaginal, laparoscopic, and hysteroscopic surgeries. It is modified and described as high, standard, or low lithotomy positions (Fig. 40-6). Dorsal lithotomy may be associated with injury to several nerves derived from the lumbosacral plexus, including the femoral, sciatic, and peroneal nerves. For example, compression and ischemic injury of the femoral nerve beneath the rigid inguinal ligament can follow prolonged sharp flexion, abduction, and external hip rotation in dorsal lithotomy (Fig. 40-7) (Ducic, 2005; Hsieh, 1998). Ideal positioning as shown can minimize these injuries.

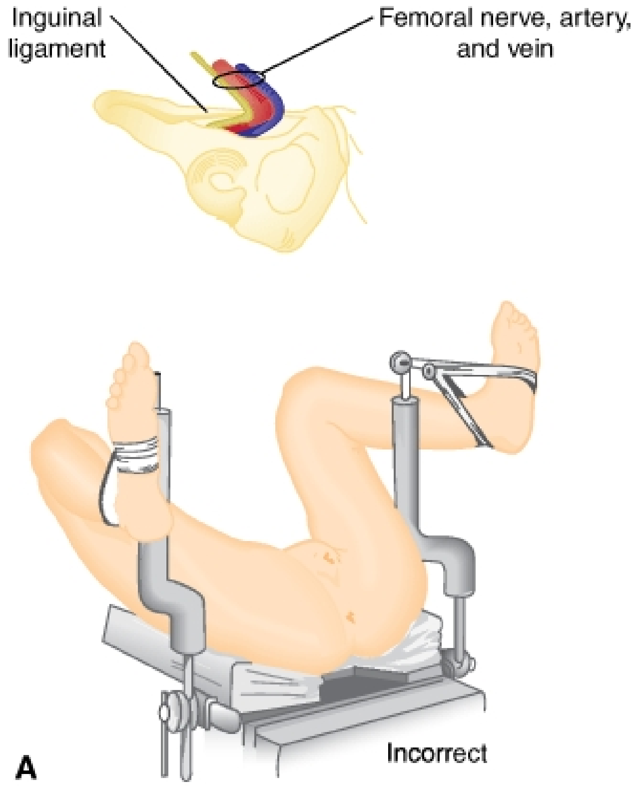
FIGURE 40-6



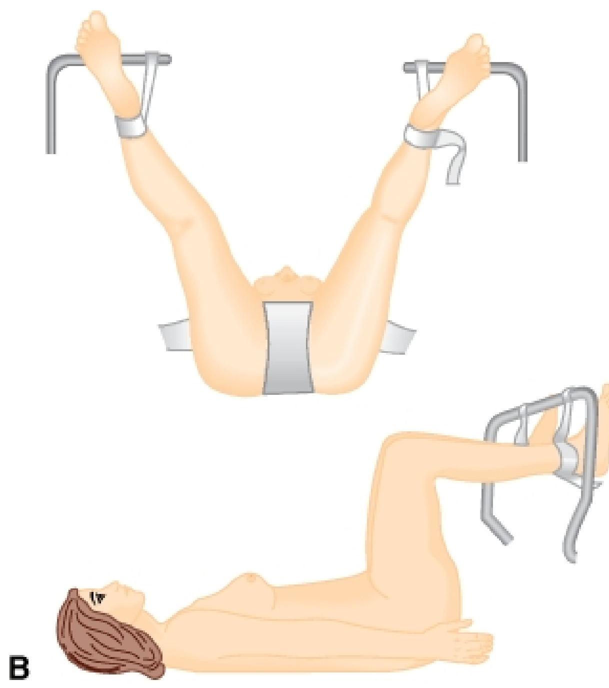
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Lithotomy positions used in gynecologic surgery. *(From Warner, 2000, with permission.)*

FIGURE 40-7



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

A. Hypeflexion of the hip can lead to compression of the femoral nerve against the inguinal ligament. *(From Anderton, 1988, with permission.)* **B.** Ideal dorsal lithotomy positioning with limited hip flexion, abduction, and external rotation. *(From Irvin, 2004, with permission.)*

SCIATIC NERVE

Derived from the lower sacral plexus, this nerve exits the pelvis through the greater sciatic foramen. It extends down the posterior thigh and branches into the tibial nerve and common peroneal nerve above the popliteal fossa. The sciatic and common peroneal nerves are anatomically fixed at the sciatic notch and head of the fibula, respectively. Thus stretch injury to the sciatic nerve can develop if a patient's hips are placed in sharp flexion or pronounced external rotation or both. Moreover, even an appropriately positioned patient may be injured if a surgical assistant during vaginal surgery leans against the thigh and creates extreme hip flexion.

The sciatic nerve contains tibial and common peroneal divisions, and injury may reflect impaired function of the entire sciatic nerve or only the common peroneal division. If the entire nerve is injured, impaired hip extension, knee flexion, and foot flexion is seen. In addition, sensory loss of the foot may be noted (McQuarrie, 1972). If only the common peroneal division is injured, then losses reflect those described in the next section.

COMMON PERONEAL NERVE

Now also termed the *common fibular nerve,* the common peroneal nerve is a lateral branch of the sciatic nerve. From its origin above the popliteal fossa, this nerve crosses the lateral head of the fibula before it descends down the lateral calf. At the lateral fibular head, this nerve is at risk for compression against leg stirrups. Therefore, patient positioning that avoids pressure at this point or the addition of cushioned padding is warranted (Philosophe, 2003).

Injury to the common peroneal nerve may have motor and sensory consequences. An inability to flex or evert the foot, or extend the toes may be noted as a "foot drop" with walking. Sensory loss encompasses the foot dorsum and anterolateral leg (Tikoo, 1994).

SURGICAL INCISIONS

In women for whom laparotomy is selected, an ideal abdominal incision allows rapid entry, affords adequate exposure, permits early ambulation, promotes strong wound healing, does not compromise pulmonary function, and maximizes cosmetic results. These criteria should form the foundation in choosing the best incision for each patient. In gynecology, entry into the abdomen typically is achieved using a midline vertical incision or one of three transverse incisions, the Pfannenstiel, Cherney, or Maylard incisions.

Midline Vertical Incisions

These incisions are used frequently when access to the upper abdomen and generous operating space are required. They can be extended up and above the umbilicus and thus, are preferred when the preoperative diagnosis is uncertain. Moreover, simple midline anatomy allows quick entry into the abdomen and low rates of neurovascular injury to the anterior abdominal wall (Greenall, 1980; Lacy, 1994). Moreover, because of decreased midline vascularity, Nygaard and Squatrito (1996) recommended this incision in patients who have coagulopathy, decline transfusion, or are administered systemic anticoagulation.

Its greatest disadvantage stems from increased tension on the incision when abdominal muscles contract. For this reason, compared with transverse incisions, midline vertical incisions are associated with higher rates of fascial dehiscence and hernia formation and poorer cosmetic results (Grantcharov, 2001; Kisielinski, 2004).

Transverse Incisions

These incisions are used commonly in benign gynecologic surgery and provide several advantages. They follow Langer lines of skin tension and thus offer superior cosmetic results. They also carry low rates of incisional hernia (Luijendijk, 1997). In addition, their placement in the lower abdomen is associated with decreased postoperative pain and improved pulmonary function compared with midline vertical incisions. Of transverse incisions, Pfannenstiel incision typically is the simplest to perform and for this reason is

selected most commonly.

Despite these advantages, limitations are noted with transverse incisions. These incisions limit access to the upper abdomen, and they offer smaller operating space compared with midline incisions. This is especially true of the Pfannenstiel incision and results from narrowing of the surgical field by intact rectus abdominis muscle bellies, which straddle the incision (see Section 41-2, Pfannenstiel Incision).

Consequently, Cherney and Maylard incisions were developed to overcome this restriction, and to some degree, they do improve exposure (see Sections 41-3, Cherney Incision and 41-4, Maylard Incision). The Cherney incision releases the rectus abdominis muscle at its inferior tendinous insertion. This approach affords greater exposure of pelvic organs as well as access to the space of Retzius. Its use therefore is considered when such operating exposure is needed.

Alternatively, the Maylard incision transects the rectus abdominis muscle and provides greater operative exposure and maneuvering space. However, it is technically more difficult to perform because isolation and ligation of the inferior epigastric arteries are required. The incision is used infrequently because of concerns regarding greater postoperative pain, decreased abdominal wall strength, longer operating times, and increased febrile morbidity. Randomized studies, however, have not supported these concerns (Ayers, 1987; Giacalone, 2002).

Incision Creation

Entry into the abdomen begins with scalpel incision of the skin, and scars should be excised to improve wound healing and cosmetic results. Although an electrosurgical blade may be used to incise the skin, faster healing and improved appearance in general follow scalpel incision (Hambley, 1988; Singer, 2002b). For the remaining layers, scalpel or electrosurgical blade may be selected, and investigations have found no differences in short- or long-term wound healing if either is chosen (Franchi, 2001). However, in evaluating surgical bleeding and postoperative pain, Jenkins (2003), in his review, noted an advantage with electrosurgical blade use.

WOUND CLOSURE

Following laparotomy, closure of a laparotomy incision must address the peritoneum, fascia, subcutaneous layer, and skin. Wound closure may be broadly categorized as either primary or secondary. With primary closure, materials are used to approximate tissue layers. In secondary closure, wound layers remain open and heal by a combination of contraction, granulation, and epithelialization. Secondary closure is used infrequently in gynecologic surgery and typically is indicated if tissues planned for closure contain significant infection. Thus, most wounds are closed primarily, as discussed below.

Optimal closure of laparotomy is the subject of much debate. Most data on the subject stem from general surgery studies on midline abdominal incision closure and from obstetric investigations of cesarean delivery technique. Ideally, closure avoids wound infection, dehiscence, and hernia or sinus tract formation yet minimizes patient discomfort.

Peritoneum

Neither visceral nor parietal peritoneum requires suturing because this layer typically regenerates within days following surgery (Lipscomb, 1996). Several studies have shown that nonclosure of the peritoneum compared with closure decreases operating time without increasing adhesion formation, wound complications, or infection (Franchi, 1997; Gupta, 1998; Tulandi, 1988).

Adhesions may commonly develop between the peritoneum and adjacent organs following surgery. Scarring can be reduced by attention to delicately handling tissues, achieving hemostasis, and by minimizing tissue ischemia, infection, and foreign-body reaction (Practice Committee of the American Society of Reproductive Medicine, 2007)

Fascia

Thus, in many cases, the first tissue closed is fascia. Many studies have supported the use of a continuous running-stitch closure of abdominal incisions compared with interrupted closure of the fascia (Colombo, 1997; Orr, 1990; Shepherd, 1983). Continuous closer usually is faster and associated with comparable rates of dehiscence, wound infection, and hernia formation. Suture material selection tends to favor delayed-absorbable suture compared with nonabsorbable. Delayed-absorbable sutures appear to afford

adequate wound support yet lead to less pain and lower rates of sinus tract formation (Carlson, 1995; Leaper, 1977; Wissing, 1987). Sutures should be placed approximately 1 cm apart and approximately 1 cm from the fascial edge. Stitches should appose fascial edges and allow tissues to swell postoperatively without cutting through fascia or causing avascular necrosis.

Subcutaneous Adipose Layer

Collections of blood and fluid serve as potential accelerants to bacterial growth. For this reason, investigators have addressed the use of subcutaneous layer suture closure or drains as a means to decrease hematoma and seroma collections. Most studies have investigated cesarean deliveries rather than gynecologic surgeries but have found no advantage to either practice in those with layers less than 2 cm thick. However, wound infection and fat thickness are the greatest risk factors for subcutaneous layer dehiscence (Soper, 1971; Vermillion, 2000). For patients with subcutaneous layers 2 cm or more thick, closing the subcutaneous layer has been shown to be effective (Gallup, 1996; Guvenal, 2002; Naumann, 1995).

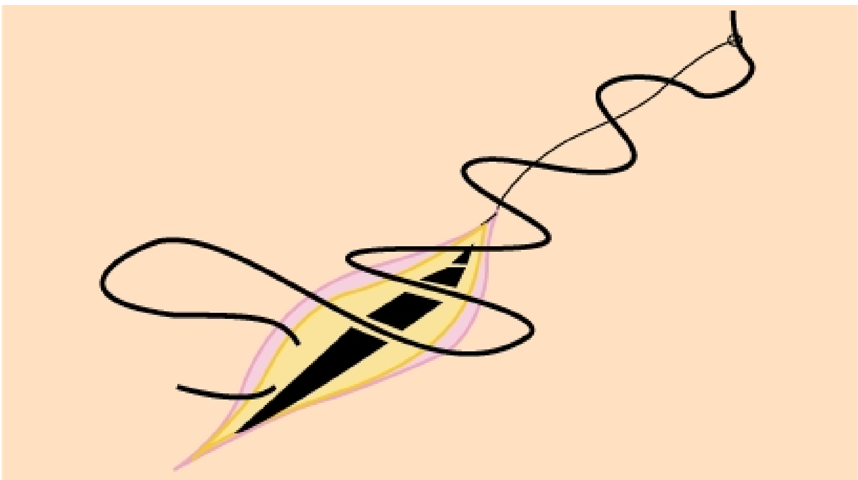
Skin

Skin may be closed effectively with staples, subcuticular suturing, adhesive wound tape, or tissue adhesive. Thus, in most instances, this layer is closed according to surgeon preference.

SUBCUTICULAR SUTURING

The running subcuticular suture is placed by taking horizontal bites through the papillary dermis on alternating sides of the wound using absorbable suture (Fig. 40-8). Advantages include decreased cost, effective skin approximation, and no required suture removal. Of skin closure techniques, however, this method typically requires the greatest amount of time and technical expertise.

FIGURE 40-8



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

During subcuticular suturing, stitches are placed with a needle horizontal to the dermis. Suturing is advanced by sequentially piercing just below the dermis on alternating sides. The spot that the first stitch exits the subcutis marks the site along the wound length that the needle should enter on the opposite side.

TOPICAL SKIN ADHESIVES

Octyl-2-cyanoacrylate (Dermabond, Ethicon, Somerville, NJ) is a topical tissue adhesive that is applied as a liquid and polymerizes to a firm, pliable film that binds to epithelium and bridges wound edges (Fig. 40-9). Appropriate for closure of skin incisions that carry minimal tension such as laparoscopy trocar or transverse laparotomy incisions, tissue adhesives achieve similar cosmetic results as traditional sutures (Blondeel, 2004; Singer, 2002a).

FIGURE 40-9

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Application of topical skin adhesive to incision. Adhesive should be placed over apposed skin edges. Application should extend out approximately 0.5 cm laterally from the incision. *(Courtesy of Ethicon, Somerville, NJ.)*

Following approximation of deeper incision layers, the adhesive is applied in three thin layers above apposed skin edges. The adhesive extends at least Â½ cm on each side of the apposed wound edges. Attention is required to avoid placement of the liquid between skin edges because the adhesive may retard healing (Quinn, 1997). Although 30 seconds between layers for drying is required, application is fast. Moreover, adhesives create their own dressing and appear to afford some antibacterial protection (Bhende, 2002). Suture or staple removal is avoided, and the adhesive sloughs in 7 to 10 days. Showering and gentle washing of the site are allowed, but swimming is discouraged. Petroleum-based products on the wound can decrease adhesive tensile strength and should be avoided.

ADHESIVE WOUND TAPE

The primary indication for tape closure is a superficial straight laceration under little tension. Thus, it is appropriate for closure of laparoscopy trocar incision sites or laparotomy incisions in which deep layer closure has brought skin edges into close proximity.

Tissue closure is fast, inexpensive, and associated with high patient satisfaction. Tapes typically are removed by the patient 7 to 10 days following surgery.

Prior to application, skin edges should be thoroughly dry for proper adhesion. Adhesive tape strips are applied in a parallel, nonoverlapping fashion after coating the entire application area with adjuvant adhesive such as tincture of benzoin (Katz, 1999). Tape may not be appropriate for a wet or oozing wound, for concave surfaces such as the umbilicus, for areas of significant tissue tension, or for areas of marked tissue laxity. Moreover, tape may separate prematurely in approximately 3 percent of cases. Importantly, skin blistering may develop if tape is stretched excessively across the wound (Lammers, 2004; Rodeheaver, 1983).

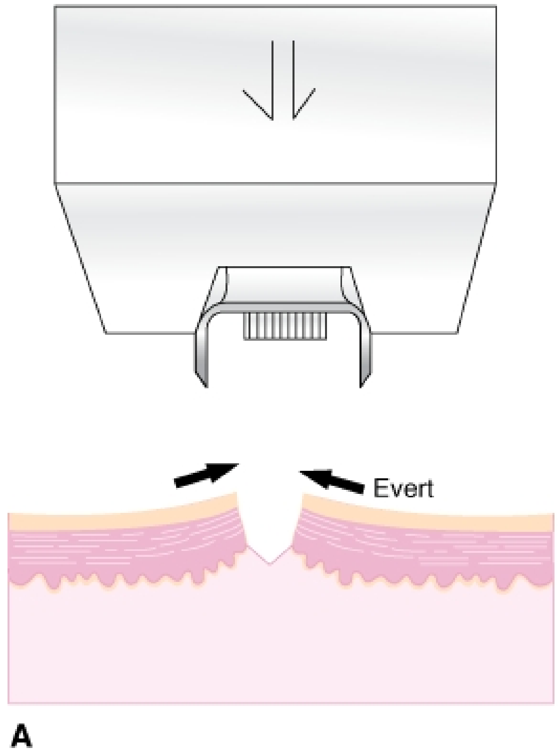
STAPLES

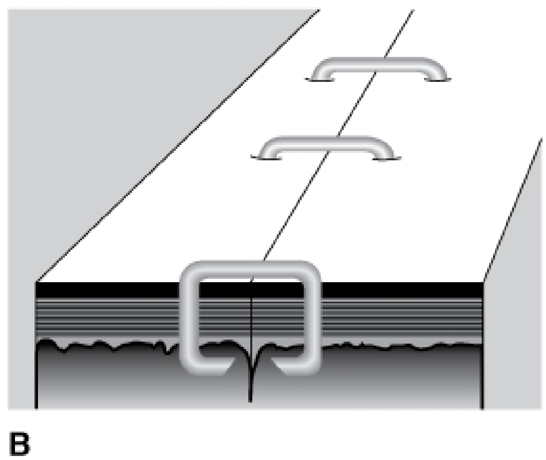
Automatic stapling devices are used commonly for surgical incisions and are favored because of their fast application and secure wound closure. However, they do not allow as meticulous a closure as sutures, and wounds requiring accurate approximation of tissue are not ideal candidates for staple closure (Singer, 1997). Staples also may be uncomfortable, may be associated with discomfort during removal, and require the patient to return for removal.

Before stapling, the wound edges should be everted, preferably by a second operator. The assistant precedes the operator along the wound and everts the wound edges with forceps. If the edges of a wound invert, or if one edge rolls under the opposite side, a poorly formed, deep, noticeable scar will result. Additionally, pressing too hard against the skin surface with the stapler should be avoided to prevent placing the staple too deeply and causing ischemia within the staple loop. When placed properly, the crossbar of

the staple is elevated a few millimeters above the skin surface (Fig. 40-10) (Lammers, 2004).

FIGURE 40-10





A. Illustration of correct staple placement. **B.** Approximately 2 to 3 mm should lie between the skin and staple crossbar. Pressure created by burying the staple into the skin may cause wound edge ischemia or painful removal. *(From Edlich, 1979, with permission.)*

INSTRUMENTS

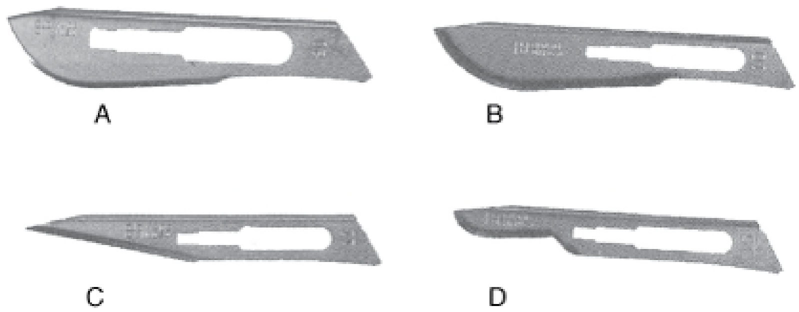
Surgical instruments have been designed to extend the capability of a surgeon's hands and thus are crafted to retract, cut, grasp,

and clear the operative field. Tissue types encountered in gynecologic surgery vary. Accordingly, so too do the size, fineness, and strength of the tools used.

Scalpel and Blades

Typical surgical blades used in gynecologic surgery are pictured in Figure 40-11 and include number 10, 11, 15, and 20 blades. Function follows form, and larger blades are used for coarser tissues or larger incisions, whereas a no. 15 blade is selected for finer incisions. The acute angle and pointed tip of a no. 11 blade can easily incise tough-walled abscesses for drainage, such as those of the Bartholin gland. During abscess drainage, the blade is drawn up and through the skin in a forward-sweeping arc.

FIGURE 40-11

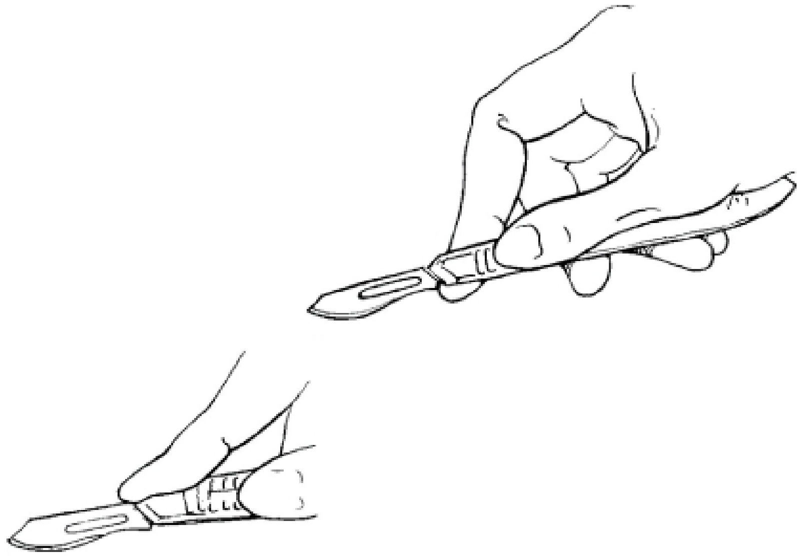


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photograph of surgical blades commonly used in gynecology. **A.** No. 20. **B.** No. 10. **C.** No. 11. **D.** No. 15. *(From Hurt, 2002, with permission.)*

With correct scalpel grasping, a surgeon can direct blade movement. Fingers may be positioned either to straddle the scalpel or to hold it as a pencil (Fig. 40-12). Incision should be made with the belly of the blade, and it is positioned perpendicular to the skin to avoid skin edge beveling. In creating long incisions such as those of the skin, a surgeon's arm moves as a smooth unit, with motion originating at the shoulder. Even pressure leads to uniform incision depth.

FIGURE 40-12



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

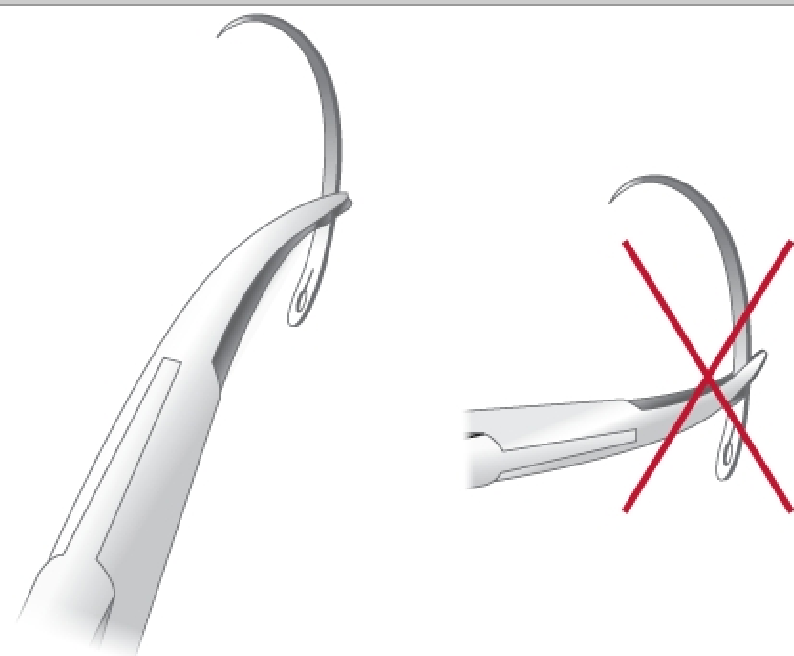
A. Scalpel is held as one would a pencil, and movement is directed by the thumb and index finger. **B.** Scalpel is held between the thumb and third finger. The index finger exerts downward pressure, and the end of the blade is forced up against the thenar muscles of the hand. *(From Wind, 1987, with permission.)*

Needle Holders

Needle holders may be straight or curved, and commonly, one with straight, blunt jaws is chosen during routine tissue approximation and pedicle ligation. Needles ideally pierce tissues perpendicularly. Thus, in most cases, the needle holder grasps a needle at a right angle and at a site approximately two-thirds from the needle tip.

Alternatively, some needle holders, such as the Heaney needle holder, are curved and aid needle placement in confined or angled areas. If a curved holder is used, the needle is grasped similarly, and the inner curve of the holder faces the needle swage (Fig. 40-13).

FIGURE 40-13



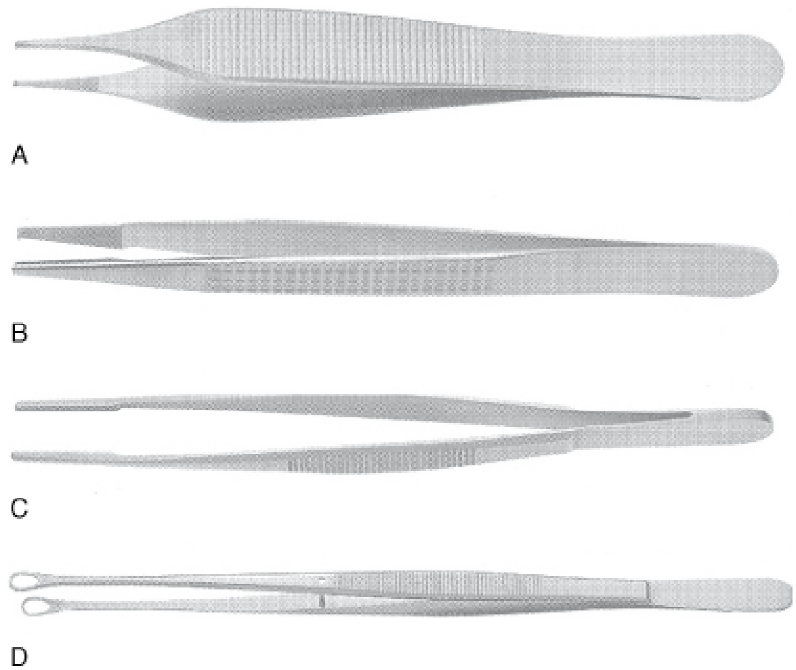
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

A. Correct grasp of a needle using a curved needle holder. **B.** Incorrect grasp. *(From Nichols, 1996, with permission.)*

Tissue Forceps

During suturing and dissection, tissues frequently are elevated or retracted with tissue forceps. Plain forceps have blunt, flat tips with shallow, fine grooves and are selected for atraumatic grasping in shallow incisions. Alternatively, a single-toothed Adson forceps provides a fine, precise grip. Its narrow, toothed tip, however, allows only a small area to be grasped and carries a greater risk of tissue tearing (Fig. 40-14). For stiffer, fibrous tissues, toothed forceps such as the Potts-Smith single-toothed forceps and Bonney forceps are preferred.

FIGURE 40-14



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Tissue forceps. **A.** Adson. **B.** Bonney. **C.** DeBakey. **D.** Singley. *(From Hurt, 2002, with permission.)*

If precise elevation of delicate tissues is needed deeper in the pelvis, then narrow-tipped, finely grooved DeBakey forceps may be chosen. In contrast, the broader, shallow-grooved tips of Russian forceps and Singley forceps may be preferred if a broader or thicker area of tissue is manipulated.

Retractors

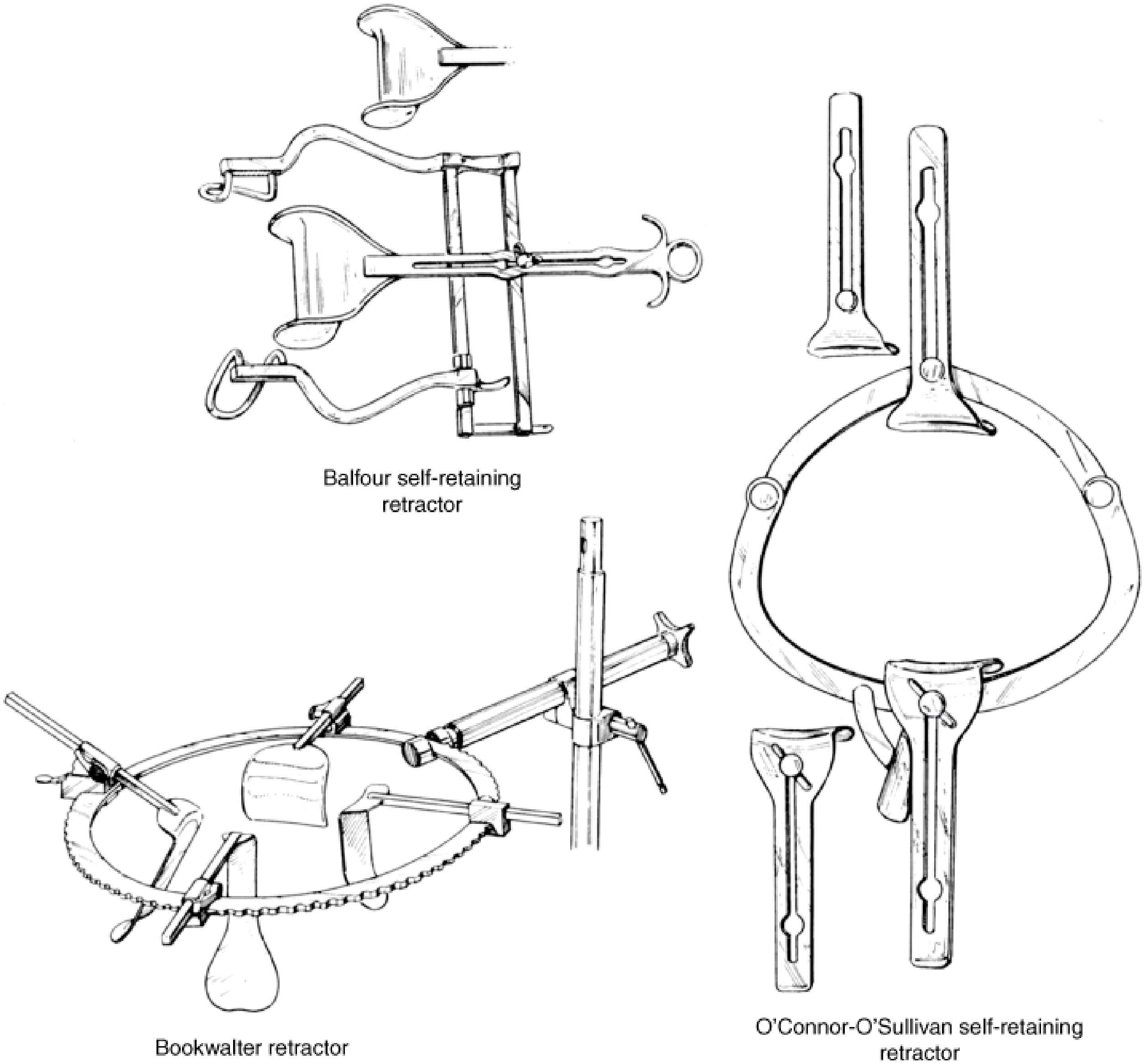
Clear visualization is essential during surgery, and retractors conform to body and organ angles to allow tissues to be pulled back from an operative field. In gynecology, retractors may be grouped broadly as self-retaining or hand-held and as abdominal or vaginal.

RETRACTORS USED IN ABDOMINAL SURGERY

Self-Retaining Retractors

Abdominal surgery often requires active participation of an assistant surgeon around a confined incision. Thus, retractors that by themselves hold abdominal wall muscles apart, termed *self-retaining,* are used commonly during laparotomy. Styles such as Balfour, Kirschner, and O'Connor-O'Sullivan contain four broad, gently curved blades and retract in four directions (Fig. 40-15). Blades pull the bladder caudally and the anterior abdominal wall muscles laterally and cephalad. Alternatively, ring-shaped retractors such as the Bookwalter and Denis Browne styles offer greater variability in the number and positioning of retractor blades. However, these usually require more time to assemble and place. With most of these styles, deep or shallow blades can be attached to the outer metal frame according to abdominal cavity depth. As discussed earlier, blades should be shallow enough to avoid compression of the femoral nerve within the psoas major muscle (Genitofemoral Nerve Injury).

FIGURE 40-15



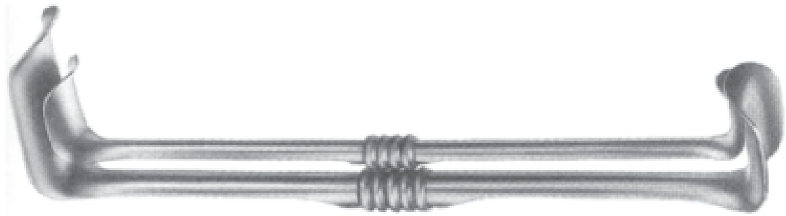
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Abdominal self-retaining retractors. *(From Lipscomb, 1997, with permission.)*

Hand-Held Retractors

Hand-held retractors may be used in addition to or in place of self-retaining styles. These instruments allow retraction in only one direction but can be placed and repositioned quickly (Fig. 40-16). The Richardson retractor has a sturdy, shallow right-angled blade that can hook around an incision for abdominal wall retraction. Alternatively, Deaver retractors have a gentle arching shape and conform easily to the curve of the anterior abdominal wall. Compared with Richardson retractors, they offer increased blade depth and are used commonly to retract bowel, bladder, or anterior abdominal wall muscles. A Harrington retractor, also called a *sweetheart retractor,* has a broader tip that also effectively holds back bowel.

FIGURE 40-16

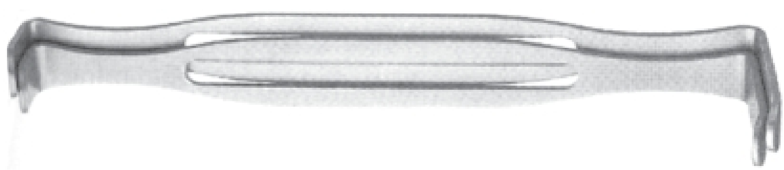


A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



C

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Hand-held retractors. **A.** Richardson. **B.** Deaver. **C.** Army-Navy. *(From Hurt, 2002, with permission.)*

In certain instances, such as during suturing of the vaginal cuff, a thin, deep retractor blade, termed a *malleable retractor,* may be required to retract or protect surrounding organs. Also called a *ribbon retractor,* this tool is a long, flexible metal strip that can be bent to conform to various body angles for effective retraction. Narrow and wider sizes are available. These also may be used to cover and protect underlying bowel from needle stick injury during abdominal wall closure.

For laparoscopy or minilaparotomy incisions, the preceding retractors are too large, and those with smaller blades such as the Army-Navy retractor or S-retractor are selected. S-retractors offer thinner, deeper blades, whereas sturdier blades of the Army-Navy style allow stronger retraction.

RETRACTORS USED IN VAGINAL SURGERY

Vaginal surgery requires separation of the vaginal walls, and several self-retaining models have been designed for this purpose. The Gelpi retractor has two narrow teeth that are placed against opposing lateral vaginal walls distally and is most appropriate for perineal procedures (Fig. 40-17). The Rigby retractor, with its longer blades, effectively separates lateral vaginal walls, whereas a Graves speculum holds apart anterior and posterior walls (see Fig. 1-4). An Auvard weighted speculum contains a long single blade

and ballasted end, which uses gravity to pull the posterior vaginal wall downward (Fig. 40-18).

FIGURE 40-17

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Vaginal self-retaining retractors. **A.** Gelpi retractor. **B.** Rigby retractor. *(From Hurt, 2002, with permission.)*

FIGURE 40-18

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Auvard weighted vaginal speculum. *(From Hurt, 2002, with permission.)*

The degree of retraction offered by vaginal self-retaining retractors, however, at times may be limited. Therefore, hand-held retractors are required often to augment or replace these instruments. Hand-held retractors used in vaginal surgery include the Heaney right-angle retractor, the narrow Deaver retractor, and the Breitsky-Navaratil retractor (Figs. 40-19 and 40-20).

FIGURE 40-19

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Right-angle retractor. *(From Hurt, 2002, with permission.)*

FIGURE 40-20

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Breisky-Navratil retractors. *(From Hurt, 2002, with permission.)*

Additionally, during vaginal procedures, the cervix often must be manipulated. Lahey thyroid clamps offer a secure grip during

vaginal hysterectomy, but their several sharp teeth can cause significant trauma. These are therefore less than ideal in patients in whom the cervix will remain. In these patients, in whom curettage or laparoscopy is performed, a single-toothed tenaculum can afford a firm grip but with less cervical damage (Fig. 40-21).

FIGURE 40-21

Single-toothed tenaculum. *(From Hurt, 2002, with permission.)*

Scissors

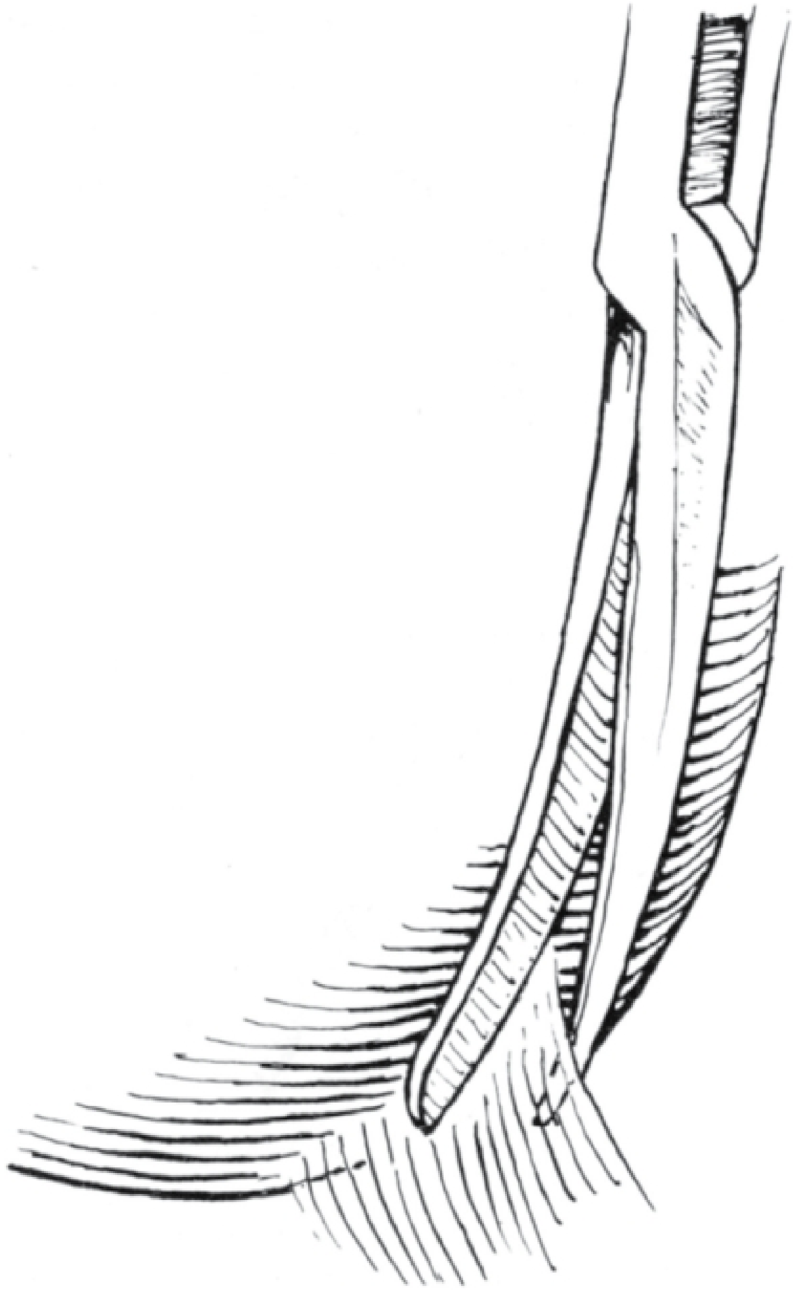
Scissors are used commonly to divide tissues, and modification in blade shape and size allows their use in a variety of tissue textures (Fig. 40-22). For correct positioning, the thumb and fourth finger are placed within the instrument's rings, and the index finger is set against the crosspiece of the scissors for greater control.

FIGURE 40-22

Scissors. **A.** Curved Mayo. **B.** Metzenbaum. *(From Hurt, 2002, with permission.)*

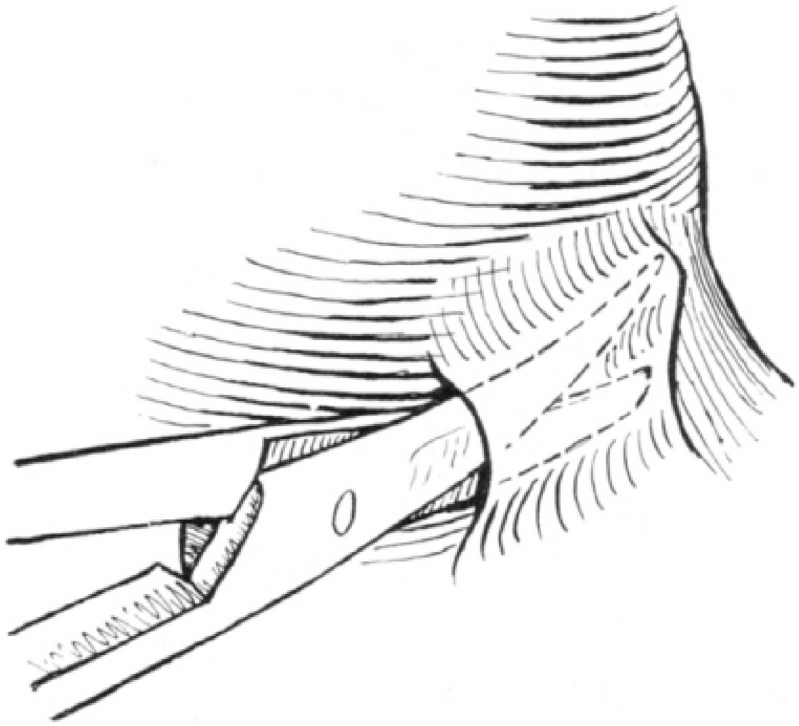
The fine blades of Metzenbaum or iris scissors are used routinely to dissect or define natural tissue planes such as dividing thin adhesions or incising peritoneum or vaginal epithelium. During dissection, traction on opposing poles of the tissue to be dissected typically simplifies the process, and a small knick is often necessary to enter the correct tissue plane. The blades are closed and inserted between planes, following the natural curves of tissues being dissected (Fig. 40-23). The blades are opened and then withdrawn. After turning both wrist and blades 90 degrees, the surgeon reinserts the lower blade, and tissues are divided.

FIGURE 40-23



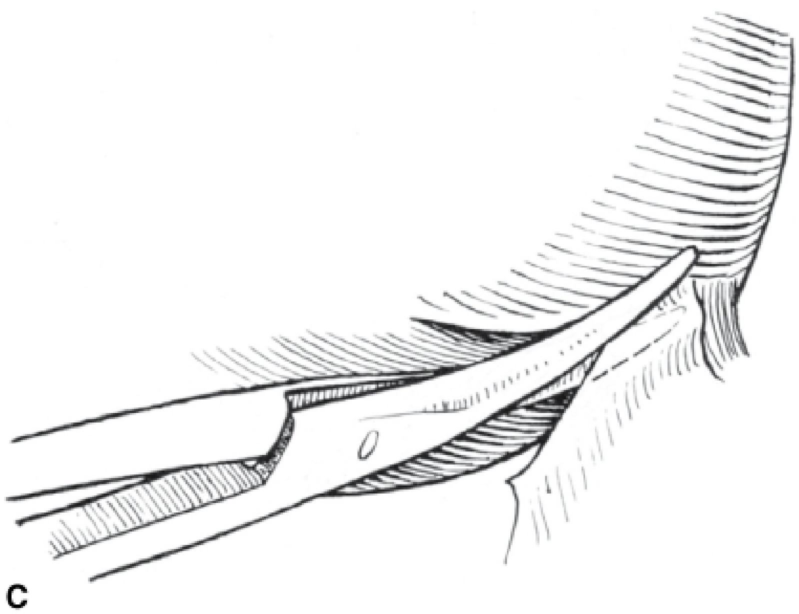
A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



C

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Metzenbaum scissors are used routinely in dissection. **A.** Dissection should proceed close to the organ surface and follows its natural curves. **B.** During development of tissue planes, the tips of closed Metzenbaum scissors are placed at the border between two tissues, and forward pressure is applied to advance the tips. **C.** The scissors are retracted and rotated 90 degrees. The lower blade is reinserted into the newly created tissue plane, and tissues are divided. *(From Wind, 1987, with permission.)*

Sturdier scissors such as curved Mayo scissors are used on thicker, denser tissues. Similarly, Jorgenson scissors have thick blades that are curved at a 90-degree angle. These are used commonly to separate vagina and uterus during the final steps of hysterectomy. Suture-cutting scissors have blunt, flat blades and should be reserved for this function. Use of tissue scissors for suture cutting often can dull their blades and should be avoided.

Tissue Clamps

Retraction is a fundamental requirement during most gynecologic surgery. As a result, variety of shapes, sizes, and strengths of clamps have been created to manipulate the different tissues encountered. For example, the smooth, cupped jaws of a Babcock clamp are ideal for gentle elevation of fallopian tubes, whereas the serrated teeth of the Allis and Allis-Adair clamps can provide a fine, firm grip on covering epithelia or serosa during dissection (Fig. 40-24 and 40-25).

FIGURE 40-24

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Babcock clamp. *(From Hurt, 2002, with permission.)*

FIGURE 40-25

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Grasping clamps. **A.** Allis-Adair clamp. **B.** Pennington. *(From Hurt, 2002, with permission.)*

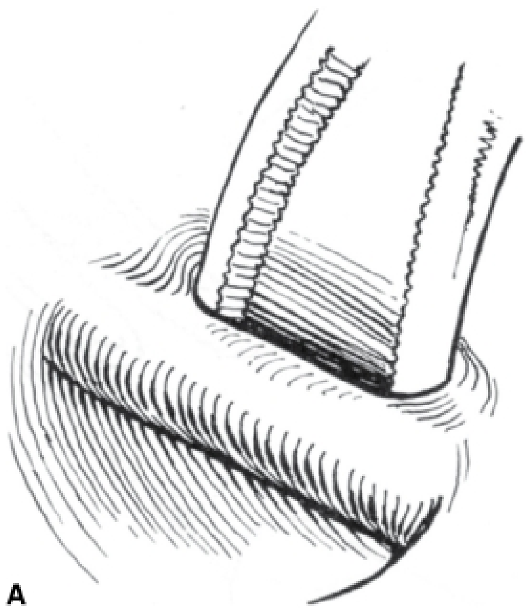
In addition to retraction, clamps are also used to occlude vascular and tissue pedicles during organ excision. Hemostats and Mixter right-angle clamps have small, slender jaws with fine inner transverse ridges to atraumatically grasp delicate tissue, especially vessels (Figs. 40-26 and 40-27).

FIGURE 40-26

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Mixter right-angle clamp *(From Hurt, 2002, with permission.)*

FIGURE 40-27

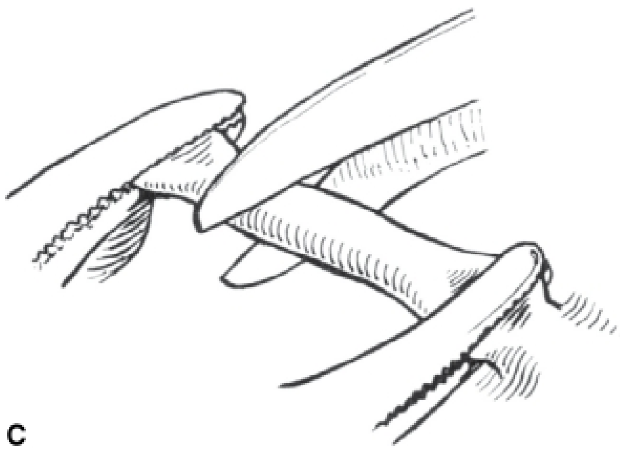


A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



C

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

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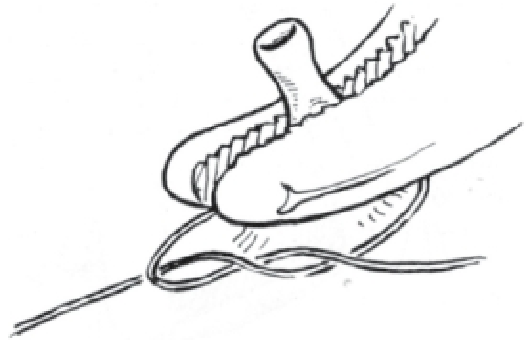


D

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Steps in vessel isolation, transection, and ligation. **A.** During vessel isolation, a clamp tip or fine scissors can be opened and closed parallel to the side of the vessel to dissect away loose surrounding tissue. **B.** The tip of the clamp is insinuated beneath the vessel, and the jaws are opened and elevated. **C.** Two clamps are placed around the vessel, and it is transected. **D.** The vessel then may be ligated with a free-tie suture placed around the clamp's tip and heel, or it may be coagulated. *(From, Wind, 1987, with permission.)*

Heavier clamps are required to grasp and manipulate stiffer tissues such as fascia or myometrium and include Kelly, Pean, Oschner, and Kocher clamps (Fig. 40-28). These clamps have finely spaced transverse grooves along their inner jaws to minimize tissue slippage. They may be straight or curved to fit tissue contours and, as with Kocher clamps, may contain a set of interlocking teeth at the tip for additional grip security. Another choice, the ring forceps, has large circular jaws with fine transverse grooves. These may be used to grasp broad, flat surfaces. Additionally, a folded gauze sponge can be placed between its jaws and used to absorb blood from the operative field or gently retract tissues.

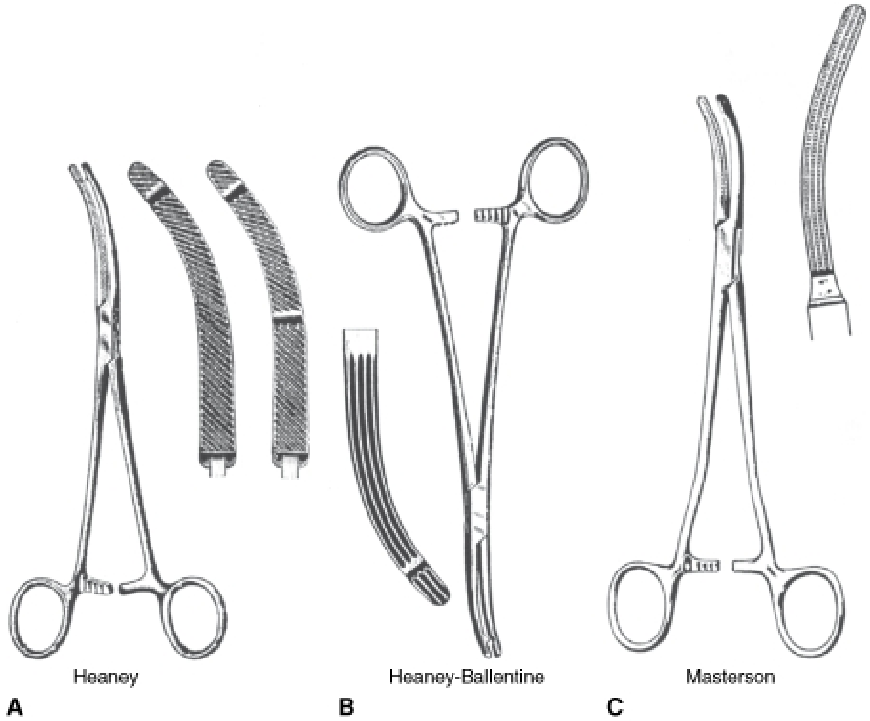
FIGURE 40-28

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Kocher clamp. *(From Hurt, 2002, with permission.)*

Ligaments that support the uterus and vagina are fibrous and vascular. Thus, a sturdy clamp that resists tissue slippage from its jaws is required during hysterectomy. A number of clamps, including Heaney, Ballantine, Rogers, Zepplin, and Masterson clamps, among others, are effective (Fig. 40-29). The thick, durable jaws of these clamps carry deep, finely spaced grooves or serrations arranged either transversely or longitudinally for secure tissue grasping. Additionally, some contain a set of interlocking teeth at the tip or heel or both. Although this modification improves grip, it also may increase tissue trauma.

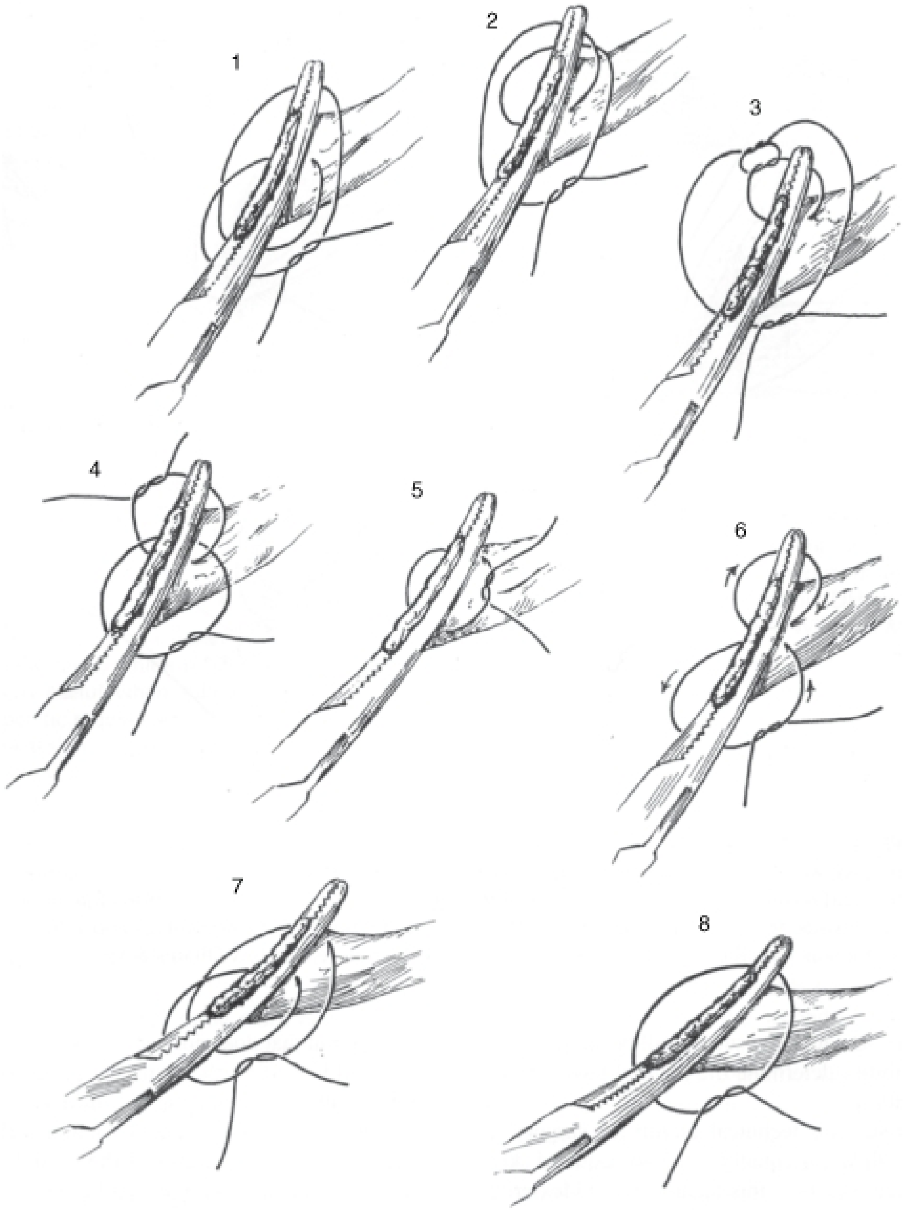
FIGURE 40-29



Heavy tissue clamps. **A.** Heaney. **B.** Heaney-Ballantine. **C.** Masterson. *(From Lipscomb, 1997, with permission.)*

Securing tissue pedicles may be accomplished using a variety of suturing techniques. A single tie alone may be placed around the pedicle, as in Figure 40-27D. In addition, a second distal transfixing suture may be placed to minimize dislodgement of the suture by vessel pulse pressures or pedicle manipulation (Fig. 40-30).

FIGURE 40-30



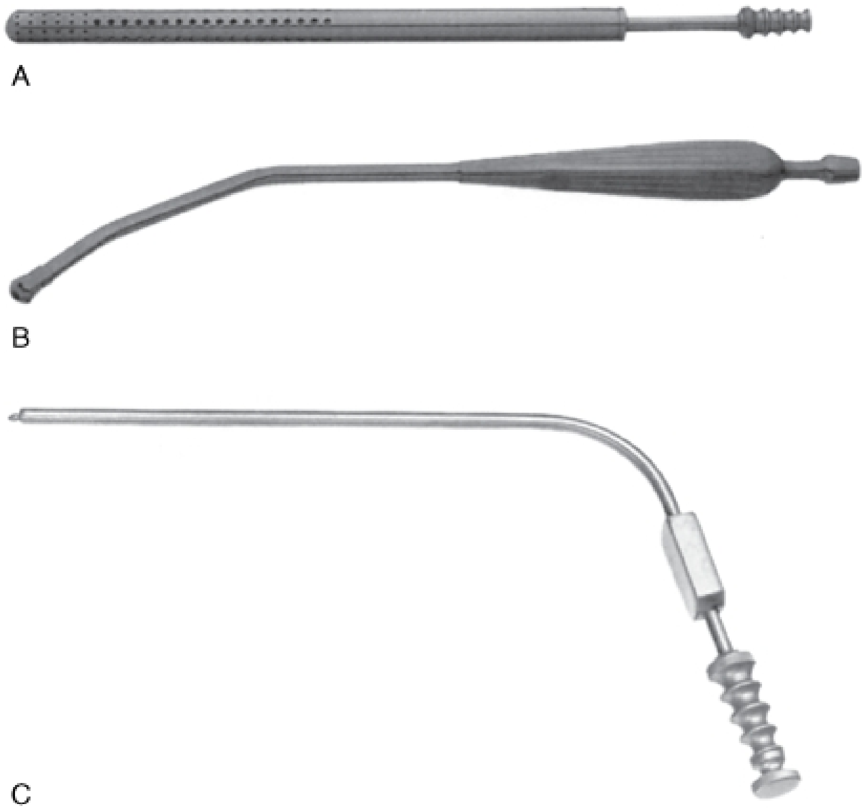
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Eight different pedicle ligation techniques. All are transfixing ligatures except for no. 8. *(From Nichols, 1978, with permission.)*

Suction Tips

During gynecologic surgery, bleeding, peritoneal fluids, pus, ovarian cyst contents, and irrigants may obscure the operating field. Accordingly, choice of suction tip typically is dictated by the type and amount of fluid encountered. Adson and Frazier suction tips are fine bore and are useful in shallow or confined areas and when little bleeding is noted (Fig. 40-31). Alternatively, a Yankauer suction tip offers a midrange-sized tip and is used commonly in general gynecology cases. However, if a larger volume of fluid or blood is expected, then a Poole suction tip may be desired. Its multiple pores allow continued suction even if some are obstructed with clot or tissue. Although it removes large volumes of fluid quickly, the sieved sheath may be removed, and the thinner-bore inner suction cannula can be used for finer suctioning. Larger-bore Karman suction cannulas are used for products of conception evacuation and are discussed in Section 41-17, Suction Dilatation and Curettage.

FIGURE 40-31



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Suction tips. **A.** Poole. **B.** Yankauer. **C.** Frazier. *(From Hurt, 2002, with permission.)*

KNOTS, SUTURES, AND NEEDLES

These are foundational tools of tissue approximation, vessel ligation, and wound closure. They are crafted in a variety of strengths, shapes, and sizes to meet surgical needs. Appropriate selection can profoundly affect wound healing and patient recovery. Thus, surgeons should be familiar with their characteristics and most appropriate applications.

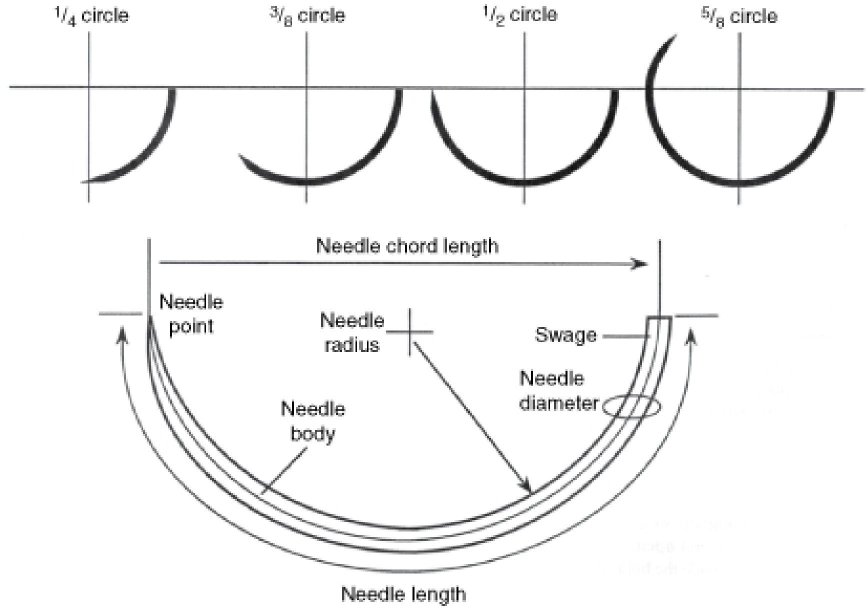
Needles

The ideal surgical needle pierces tissue with ease, with minimal tissue damage, and without bending or breaking. Tissues differ in their density and location, and thus needles are designed with variable sizes, shapes, and tips.

NEEDLE CONSTRUCTION

The anatomy of a needle is simple, and each contains a tip, body, and site of suture attachment (Fig. 40-32). For most gynecologic cases, the suture and needle used are attached as a continuous unit, which is described as *swaged.* This contrasts with needles that have eyes for suture threading. Swaged needles may be firmly secured to the suture and require cutting at the end of suturing. Alternatively, *controlled-released,* or "pop-off", swaged needles detach from the suture with a brisk tug. Controlled-release needles are used commonly when securing vascular pedicles or placing interrupted sutures. Continuous running suturing typically requires a swaged needle without the controlled-release feature.

FIGURE 40-32



Various needle configurations and characteristics of a curved surgical needle. *(Modified from Dunn, 2005, with permission.)*

In certain urogynecologic procedures, such as abdominal sacrocolpopexy, *double-armed suture* is often chosen. This suture contains identical swaged needles at each of its ends. This design enables surgeons to suture distant tissues with different ends of the suture before approximating them.

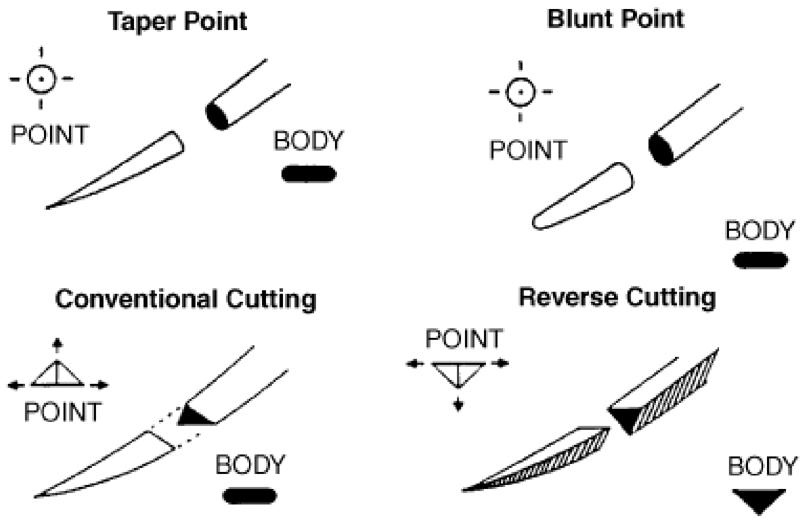
Descriptors of needle size and shape are noted in Figure 40-32. Of these, needle radius, circle configuration, and gauge more frequently influence surgical selection. For example, a needle should be large enough to pass completely through the tissue and exit far enough to allow the needle holder to be repositioned on the end of the needle at a safe distance from the tip. Repeated grasping of the needle tip leads to a dulled tip. This subsequently leads to difficult tissue penetration and greater tissue trauma.

For thicker tissues, a larger radius and gauge are warranted. For confined surgical spaces, a needle with smaller radius and greater circle configuration typically is required. Thus, for most gynecologic procedures, a three-eights or one-half circle configuration is used. For some urogynecologic operations, a five-eights circle configuration is preferred.

NEEDLE POINT

The tip should allow passage of the needle through tissue with the smallest degree of tissue damage. Those with tapered points are used for suturing thin tissues, such as peritoneum (Fig. 40-33). Alternatively, cutting needles are preferred for denser tissue such as fascia and ligaments.

FIGURE 40-33



Configurations of various needle tips and bodies. *(Modified from Dunn, 2005, with permission.)*

Cutting points have sharp edges laterally and a third sharp edge extending either toward or away from the needle's inner curve. A conventional cutting needle features the third cutting edge on the inside curve and provides shallower tissue bites. In contrast, reverse cutting needles have the third cutting edge directed away from the inner curve of the needle and are used for particularly tough tissues.

Sutures

Sutures should maximize wound healing and tissue support. Thus, surgeons should be familiar with the qualities of a particular suture for a given clinical setting (Table 40-3 and 40-4). In addition, sutures may be categorized by their biologic or synthetic derivation, their filamentous structure, and their ability to be degraded and reabsorbed.

Table 40-3 Characteristics of Suture Material
I. **Physical characteristics**
Physical configuration
Capillarity
Fluid absorption ability
Diameter (caliber)
Tensile strength
Knot strength
Elasticity
Plasticity
Memory
II. **Handling characteristics**
Pliability

Tissue drag Knot tying Knot slippage
III. **Tissue reaction characteristics** Inflammatory and fibrous cell reaction Absorption Potentiation of infection Allergic reaction

From Bennett, 1988, with permission.

Table 40-4 Specific Suture Material Characteristics

Type	Configuration	Tensile Strength	Handling	Knot Security	Reactivity
Nonabsorbable					
Silk	Braided	Good	Good	Good	High
Nylon	Monofilament	High	Fair	Fair	Low
Prolene	Monofilament	Good	Poor	Poor	Low
Mersilene	Braided synthetic	High	Good	Good	Moderate
Ethibond	Braided, coated	High	Fair	Fair	Moderate
Stainless steel wire	Monofilament	High	Poor	Good	Low
Novafil	Monofilament	High	Fair	Poor	Low
Absorbable					
Gut (plain)	Twisted	Poor	Fair	Poor	Low
Chromic (gut)	Twisted	Poor	Fair	Poor	High
Dexon	Braided	Good	Good	Good	Low
Vicryl	Braided	Good	Good	Fair	Low
PDS II	Monofilament	Good	Fair	Poor	Low
Monocryl	Monofilament	Fair	Good	Good	Low

From Cunningham, 2002, and Stanton, 1982, with permission.

BIOLOGIC OR SYNTHETIC SUTURES

Sutures such as catgut, silk, linen, and cotton are derived from biologic sources. As a group, biologic sutures produce the greatest

tissue reaction and have the lowest tensile strength profile. Accordingly, most suture materials currently used in gynecologic surgery are synthetic.

MONOFILAMENT OR MULTIFILAMENT SUTURE

The number of strands that comprise a given suture defines it either as *monofilament* or *multifilament.* Monofilament suture is constructed as a single strand, whereas multifilament suture contains multiple strands that are braided or twisted. Monofilament sutures have lower friction coefficients and therefore pull more easily through tissues, and as a result, create less tissue injury. As a group, they tend to incite less tissue reaction. Moreover, braid crevices are absent, and bacteria therefore are less likely to adhere (Bucknall, 1983; Sharp, 1982). However, monofilament sutures are in general less pliant for knot tying and, if knicked by instruments, are more prone to breakage.

ABSORBABLE OR NONABSORBABLE SUTURE

The rate at which tensile strength is lost differentiates suture types, and suture that has lost most of its tensile strength by 60 days following surgery is considered to be *absorbable* (Bennett, 1988). Absorbable suture is destroyed enzymatically or hydrolyzed, whereas nonabsorbable suture persists and ultimately is encapsulated.

Ideally, absorbable suture material remains throughout wound healing but no longer. Individual tissue characteristics typically dictate whether short- or long-term sutures are required for adequate wound healing. Thus, nonabsorbable suture is indicated when long-term approximation or support is required. Accordingly, nonabsorbable material plays a greater role in pelvic floor reconstruction procedures, whereas absorbable suture is used routinely in general gynecologic surgery.

REACTIVITY

All sutures, when placed within tissue, will incite inflammation. This response mirrors the total amount of suture placed and the suture's chemical composition (Edlich, 1973). In general, lower inflammatory responses are elicited by monofilament structure compared with multifilament, and synthetically derived compared with natural fiber (Lin, 2006; Sharp, 1982).

CAPILLARITY AND FLUID ABSORPTION

The ease of fluid to wick from the wet end of a suture to its dry end defines its *capillarity.* A suture's *fluid absorption ability* describes the amount of fluid it absorbs when immersed. Both properties are presumed to have an impact on the access of contaminating bacteria. Increased capillarity and fluid absorption ability greatly increase the amount of bacteria similarly absorbed (Blomstedt, 1977). In general, multifilament sutures, even those with coatings, display greater capillarity compared with synthetic monofilament sutures (Geiger, 2005).

CALIBER

The diameter of a suture reflects its size and is measured in tenths of a millimeter. A midpoint diameter size is designated as 0, and as suture diameter increases above this, arabic numbers are assigned. For example, no. 1 catgut is thicker than 0 catgut.

As suture diameter decreases from this midpoint, 0s are added. By convention, an arabic number followed by a 0 also may be used to reflect the total number of 0s. For example, 3-0 suture also may be represented as 000. Moreover, 3-0 suture is greater in diameter than 4-0 (0000) suture.

Ideally, the appropriate suture caliber is small enough to limit tissue damage during placement and minimize subsequent tissue reaction yet provide ample tensile strength to support and approximate involved tissues.

TENSILE STRENGTH

Defined as the amount of weight necessary to break a suture divided by its cross-sectional area, *tensile strength* is an important characteristic for suture selection. Ideally, the tensile strength of material chosen should approximate the strength of the tissues being sutured.

ELASTICITY, PLASTICITY, MEMORY

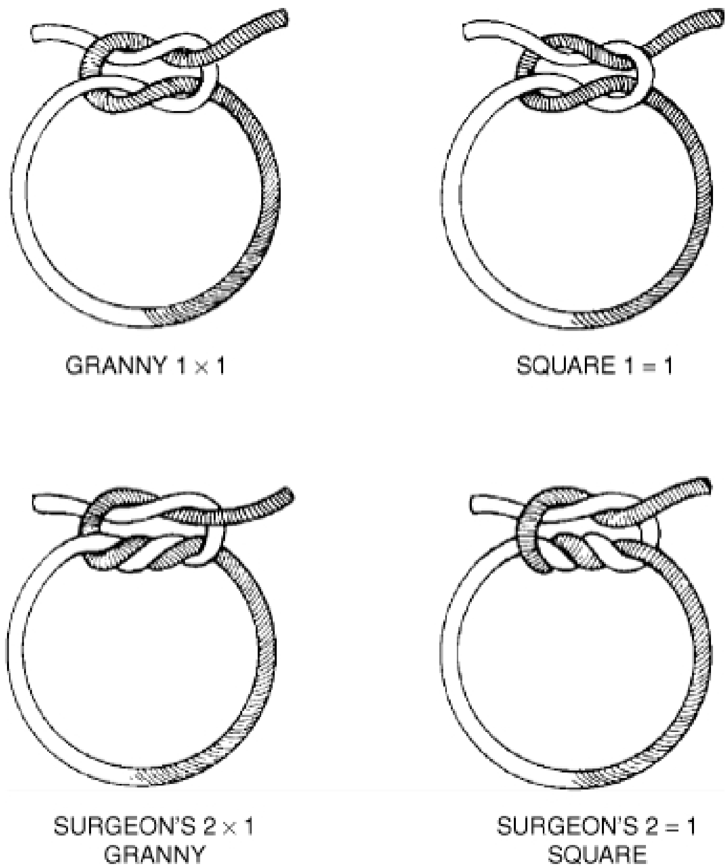
The ability of a material to return to its prior length following stretch defines its *elasticity. Plasticity,* however, describes the

tendency of material to retain its new shape once stretched. For tissues in which swelling or movement is expected postoperatively, a suture with increased elasticity is preferred because it will stretch rather than cut into approximated tissues. *Memory* defines the ability of material to return to original form following deformation. Sutures with greater memory tend to untie more easily during knot tying.

Knots

In gynecologic surgery, knots secure sutures during vessel ligation, creation of reconstructive support, and incision reapproximation. A number of knotting styles are available to the surgeon, but square knot, surgeon's knot, and slip knot are used most commonly (Fig. 40-34).

FIGURE 40-34



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Surgical knots. *(From Cunningham, 2002, with permission.)*

The number and type of knots required to secure various suture material vary, and qualities such as elasticity, plasticity, and memory often direct these recommendations. In general, multifilament sutures are easier to handle and display less memory. For these, square knots are appropriate. Synthetic monofilament suture materials or multifilament sutures with coatings, however, have increased memory and may hold a knot poorly. Thus, a surgeon's knot typically is recommended. In addition, each additional throw of a knot up to a certain point adds security. After this threshold, additional throws only serve to increase suture breakage and to act as a nidus for infection.

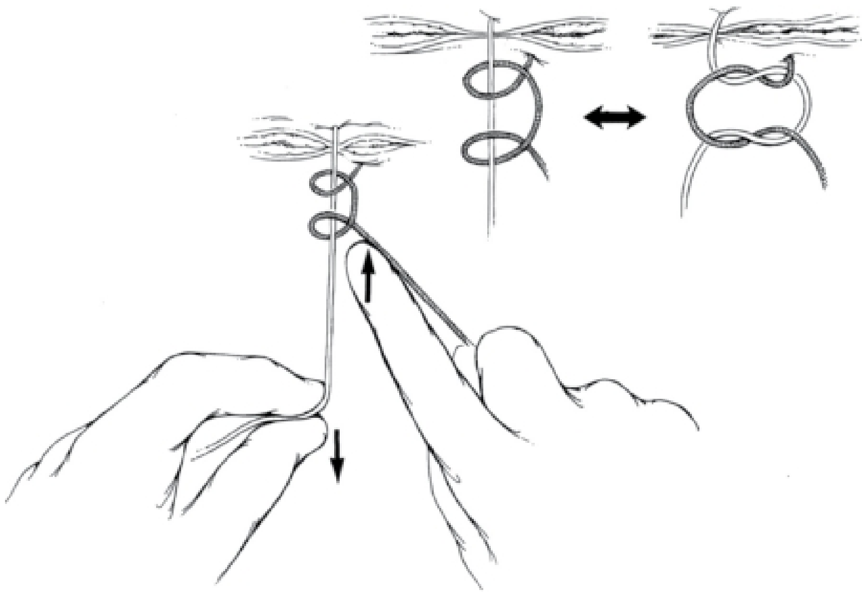
In characterizing knots, each loop is given a numerical description. Loops with a single throw are noted as 1, whereas a loop with

two throws, as in a surgeon's knot, is assigned the number 2. If successive loops are identical, as with a granny knot, then a multiplication sign is placed between loop numbers. If loops mirror one another, as in the square knot, then an equal sign is used. Thus a square knot is described as 1 = 1; granny knot, 1 × 1; and square surgeon's knot, 2 = 1.

Knots are typically the weakest part of any suture, and the force necessary to break a knotted suture is less than that to break an individual suture strand. In addition, knot strength is affected by the speed at which force is applied to the knot. Abrupt tightening of knots may break sutures more easily than slowly securing them.

Of those used by gynecologists, square knots are considered the strongest, followed by surgeon's and granny knots. Slip knots are the weakest but are used often of necessity by gynecologists. Deep, narrow operating spaces may limit the hand crossing needed for square knotting (Fig. 40-35). If slip knots are placed initially to approximate tissue, they should be converted to square knots or reinforced with a square knot once the pedicle or vessel is secured.

FIGURE 40-35



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

A slip knot can be converted to a square knot by applying tension primarily to one suture end. *(Modified from Edlich, 2005, with permission.)*

ELECTROSURGERY

Electrosurgery is one of the most commonly used surgical tools and enables surgeons to coagulate vessels and incise tissues rapidly. Familiarity with its basic principles can increase its effective use and minimize tissue injury.

Semantically, *electrosurgery* differs from *electrocautery,* although the terms are often incorrectly interchanged. Electrocautery is not used commonly in gynecologic surgery, and with it, electric current passes through a metal object, such as a wire loop, with internal resistance. Passage of the current through the resistance heats the loop, which then may be used surgically. The flow of current is limited to the metal being heated, and no current enters surgical tissues.

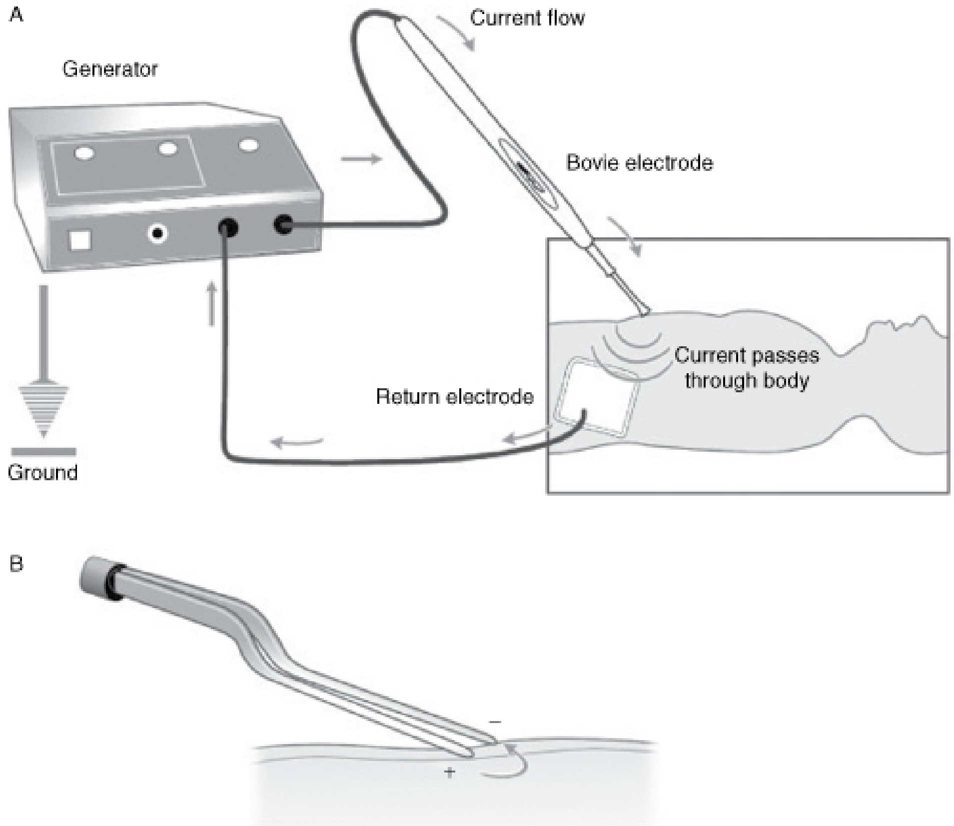
In contrast, electrosurgery directs the flow of current to the tissues themselves and produces localized tissue heating and destruction. As a result, electric current must pass through tissues to produce the desired effect (Amaral, 2005).

Monopolar Electrosurgery

Electric current is the flow of electrons through a circuit (Fig. 40-36). Voltage is the force that drives those charges around the circuit. Impedance is the combination of resistance, inductance, and capacitance that alternating current meets along the way

(Morris, 2006). In surgery, the electrosurgical circuit consists of four primary parts: the electrosurgical generator, active electrode, patient, and return electrode, which in clinical use is the grounding pad. Current flows: (1) from the generator, which is the source of voltage, (2) through the electrosurgical tip to the patient, the source of impedance, and then (3) onto the grounding pad, where it is dispersed. Current leaves the pad to return to the generator, and the circuit is completed (Deatrick, 2006).

FIGURE 40-36



Circuits in electrosurgery. **A.** Monopolar electrosurgical circuit. **B.** Bipolar electrosurgical circuit. *(From Deatrick, 2006, with permission.)*

In electrosurgery, tissue impedance converts electric current into thermal energy that causes tissue temperatures to rise. It is these thermal increases that create electrosurgery's tissue effects.

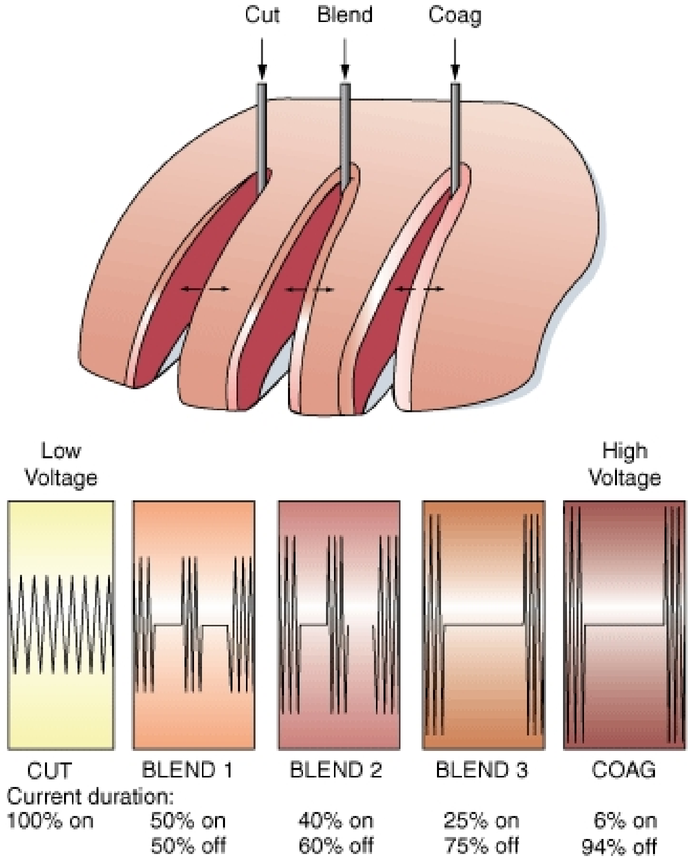
The current from a wall outlet that powers electrosurgical generators has a frequency of 60 Hz (in the United States) or 50 Hz (in other parts of the world). Extreme neuromuscular stimulation can result from this lower frequency, as with electrocution. However, at frequencies above 100 Hz, excitable membranes are not depolarized, and thus nerve and muscles responses are bypassed. For safe use during electrosurgery, modern surgical generators increase frequencies to greater than 200 Hz (Valleylab, 2006).

Surgical Effects

Differing tissue effects are created by altering the manner in which current is produced and delivered. First, altering the current wave pattern can affect tissue temperatures. For example, the high-frequency continuous sinusoidal waveform produced with cutting current creates higher tissue temperatures than that with coagulation current (Fig. 40-37). Second, the extent to which current is spread over an area, also termed *current density,* alters the rate of heat generation. Thus, if current is concentrated onto a small area such as a needle-tip electrode, greater tissue temperatures are generated than if delivered over a wider area such as an electrosurgical blade. In addition to current density, voltage can alter tissue effects. As seen in Figure 40-37, as voltage

increases, the degree of thermal tissue damage similarly increases. And finally, the qualities and impedance of the tissues themselves affect energy transfer and heat dissipation. For example, water has low electrical impedance and liberates little heat, whereas skin with its greater impedance generates significantly higher tissue temperatures (Amaral, 2005).

FIGURE 40-37



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Tissue effects vary with cutting, blended, and coagulation currents. There is more lateral thermal damage with a pure coagulation current compared with a pure cutting or blended current. The duration of applied energy varies between current types.

CUTTING CURRENT

With electrosurgical cutting, a continuous sine wave of current is produced. The flow of high-frequency current typically is concentrated through an electrosurgical needle or blade and meets tissue impedance. Sparks are created between the tissue and electrode, intense heat is produced, cellular water vaporizes, and cells in the immediate area burst. Tissues are cut cleanly, and there is minimal coagulum production. As a result, few vessels are sealed, and minimal hemostasis accompanies electrosurgical cutting.

COAGULATION CURRENT

In contrast with cutting current, coagulation current does not produce a constant waveform. Less heat is produced than with cutting current. However, tissue temperature still rises sufficiently to denature protein and disrupt normal cellular architecture. Cells are not vaporized instantly, and cellular debris remains associated with wound edges. This coagulum seals smaller blood vessels and controls local bleeding (Singh, 2006).

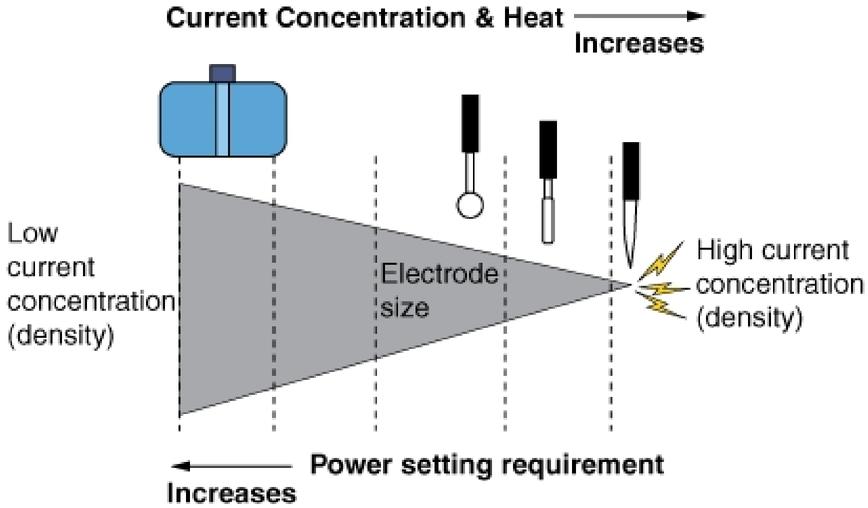
BLENDED CURRENT

Variations in the percentage of time that current is flowing can create electrosurgical effects that contain both cutting and coagulating features. Such *blended currents* are used commonly in gynecologic surgery. In most cases, selection of specific percentages of cutting and coagulation current is affected by surgeon preference and type of tissues encountered. Thinner vascular tissue may be best suited for a blend with less active current time, whereas denser avascular tissues may require a greater percentage of active current.

Patient Grounding

As discussed earlier, current is concentrated at the electrode tip and enters the patient at a small site. Current follows the path of least resistance and exits the body through a grounding pad that is designed to have a large surface area, high conductivity, and low resistance (Fig. 40-38). Dissipation across this large surface area allows current to leave the body without generating significant tissue temperatures at the exit site.

FIGURE 40-38



Current concentration and its effects. Thermal energy and risk for tissue injury diminish as current density decreases and electrode area increases.

However, patient burns may result if current is again concentrated through a return electrode. Clinically, this may occur if a grounding pad is partially dislodged. In this setting, the surface area is decreased, and exiting current concentration and tissue temperatures at the exit site rise. In addition, patient jewelry, metal candy cane stirrups, or other surfaces with high conductivity and low resistance may serve as a return electrode. In such cases, patient may be burned by concentrated current exiting through these small contact sites.

Ideally, grounding pads should be firmly adhered to a relatively flat body surface that is near the operative field. Thus, in most gynecology procedure, grounding pads are placed along the lateral upper thigh.

Bipolar Electrosurgery

This form of electrosurgery differs from monopolar electrosurgery in that the tip of a bipolar device contains both an active and a return electrode (see Fig. 40-36B). For this reason, a distant grounding return pad is not required. Coagulation current is concentrated on tissues grasped between the electrodes, and tissue must remain between them. If tissue slips from between the tips, then active and return electrodes contact and create a short circuit. Coagulation will not occur (Michelassi, 1997). Bipolar electrosurgery uses only coagulation current and lacks cutting capability. However, it is useful for vessels coagulation and also is used during laparoscopic sterilization to coagulate fallopian tubes (see Section 41-29, Laparoscopic Sterilization).

Argon Beam Coagulation

This tool represents a modification of conventional electrosurgical coagulation. With argon beam coagulation (ABC) radiofrequency energy is transferred to tissues through a jet of inert argon gas to create noncontact monopolar electrothermal coagulation. Additionally, the gas jet clears blood and tissue dÃ©bris during coagulation. Advantages of ABC include the ability to coagulate broad surface areas and larger vessels (Beckley, 2004). In gynecologic surgery, ABC is used most commonly during ovarian staging cases in which extensive debulking may be required.

Coexisting Electrical Devices

Patients with pacemakers, internal cardioverter-defibrillators (ICDs), or other electrical implants require special precautions. Stray electrosurgical current may be interpreted as an intracardiac signal by an implanted device and lead to pacing changes. In addition, myocardial electrical burns may result from conduction of current through the pacing electrode rather than through the grounding pad (Pinski, 2002).

Accordingly, for patients with these devices, preventative recommendations include pre- and postoperative cardiology consultation, use of minimal monopolar electrosurgical current settings or substitution with bipolar electrosurgery or harmonic scalpel, continuous cardiac monitoring, contingency plans for arrhythmias, and an adequate distance between the active and return electrodes (El-Gamal, 2001).

ULTRASONIC ENERGY

Sound waves are mechanical waves that transport energy through a medium. Those above audible range are described as *ultrasound* or *ultrasonic.* In medicine, ultrasound waves that are applied at low levels such as those used in diagnostic sonography are harmless. However, if higher power levels are used, then mechanical energy of sufficient strength is transferred to the impacted tissues, and cutting, coagulation, or tissue cavitation is produced.

Ultrasonic Scalpel

The tip of an ultrasonic scalpel, also known as a *harmonic scalpel,* vibrates at high frequency, allowing the surgical device to be used effectively for both cutting and coagulating during laparotomy or laparoscopy (Gyr, 2001; Wang, 2000). The vibrating tip transfers mechanical energy to tissues. Mechanical energy breaks hydrogen bonds and generates heat within tissues to denature protein and form a sticky coagulum that produces hemostasis (Amaral, 1993)

A balance between cutting and coagulation is created by controlling three factors: power levels, tissue tension, and blade sharpness. Higher power level, greater tissue tension, and a sharp blade will lead to cutting, whereas lower power, decreased tissue tension, and a blunt blade will create slower cutting and greater hemostasis (Sinha, 2003).

Used most commonly in laparoscopic surgery, the ultrasonic scalpel serves as an alternative to suture ligation, electrosurgical coagulation, laser, and stapling or clipping devices. However, only a few studies have been published comparing the clinical effectiveness of this method with other methods of hemostasis (Kauko, 1998).

Cavitational Ultrasonic Surgical Aspiration

An ultrasonic surgical aspirator hand-piece contains three main components: a high-frequency vibrator, which transfers the ultrasonic energy to tissues; irrigation tubing, which directs cooling saline to the tip; and a suction system, which draws tissue up to the tip for contact with the vibrator and which also clears away tissue fragments and irrigant. Ultrasound energy can be used to raise tissue temperatures dramatically and thereby disrupt tissue architecture by a process termed *cavitation.* With cavitation, a rapidly oscillating cavitational ultrasonic surgical aspiration (CUSA) tip produces mechanical waves that create heat and vapor pockets around cells in tissues with high water content such as fat, muscle, and carcinoma. Collapse of these pockets leads to disruption of cell architecture (Jallo, 2001). Affected tissues are removed subsequently by suction aspiration. However, tissues containing less water and higher contents of collagen and elastic fibers, such as blood vessels, nerves, ureters, and serosa, are more resistant to damage (van Dam, 1996).

In gynecology, CUSA has a limited surgical role and has been used in the treatment of vulvar intraepithelial neoplasia, bulky

condyloma accuminata, and cytoreductive ovarian cancer surgery (Aletti, 2006; Deppe, 1988; Robinson, 2000; van Dam, 1996).

MANAGEMENT OF HEMORRHAGE

Ideally, problematic bleeding is avoided during surgery by optimizing preoperative preparations, ensuring adequate operative exposure, and using proper surgical technique. However, if hemorrhage does occur, surgeons should be familiar with its appropriate management.

Optimizing Preoperative Preparations

Although the risk of hemorrhage accompanies most gynecologic procedures, certain factors are associated with higher rates of bleeding and should be assessed prior to surgery. Specifically, obesity, the presence of a large pelvic mass, adhesions such as those from endometriosis or pelvic inflammatory disease, cancer or prior radiation, and coagulation dysfunction all have been linked with an increased risk of hemorrhage. For those identified to be at risk, intraoperative red cell salvage or preoperative autologous blood donation may be considered.

RED BLOOD CELL SALVAGE

Red blood cell (RBC) salvage machines (Autolog, Medtronic, Minneapolis, MN; CATS, Fresenius, Redmond, WA; Cell Saver, Haemonetics Corp., Braintree, MA) collect, filter, and centrifuge blood lost during surgery and may be helpful in patients in whom increased intraoperative hemorrhage is anticipated. RBCs are heavier and are separated from plasma and smaller blood components during centrifugation and then reinfused into the patient. Anticoagulants such as heparin or citrate are added to prevent clotting (Karger, 2005).

Salvage efficiencies approximate 60 percent with good technique. However, vacuum levels, suction tip size, and thoroughness of salvaging efforts can affect this value. For example, turbulence destroys RBCs. Thus, suction tips with greater diameters and lower suction force can minimize hemolysis (Waters, 2005). Additionally, laparotomy sponges can be rinsed in sterile saline to maximize RBC removal. The RBC-containing saline then is suctioned into the salvage device for processing.

Filtering systems in these devices have limitations. Accordingly, RBC salvage is not appropriate for contaminated cases or those in which malignancy, hemostatic agents, or amnionic fluid may be present (Waters, 2004).

PREOPERATIVE AUTOLOGOUS DONATION

To avoid potential transfusion reaction or blood-borne infection, a patient may elect to donate her own blood for personal use approximately once a week for 3 to 5 weeks preceding surgery. Patient hemoglobin levels should be greater than 11.0 g/dL before each donation. Moreover, units should not be collected within 72 hours before surgery. This allows intravascular volume to be repleted by the patient and units to be processed by the blood bank (Goodnough, 2005). Disadvantageously, this process has been associated with preoperative anemia secondary to donation, more liberal transfusion, transfusion reaction following clerical error, volume overload, and bacterial contamination of blood products during processing (Henry, 2002; Kanter, 1996, 1999).

Improved blood banking safety has accompanied a decline in PAD (Brecher, 2002). Moreover, for most gynecologic cases, the risk of transfusion is low. For these reasons, autologous donation typically is reserved for selected instances in which the risk of transfusion is significant, such as radical hysterectomy or surgery for patients with coagulopathies. Additionally, patients with rare blood phenotypes in whom acquisition of compatible blood may be difficult may benefit from PAD.

Proper Surgical Method

In many instances, proper surgical technique may minimize vascular injury and hemorrhage. Thus, prior to ligation, vessels should have excess connective tissue removed with fine scissors in a process called *skeletonizing.* Additionally, tissue clamps selected for grasping a vascular pedicle should be large enough to contain the entire pedicle in the distal portion of the clamp. Large pedicles that force excess tissue toward the clamp heel carry greater risk of tissue slipping from the heel and bleeding. Once secure, sutures placed on vascular pedicles should not be used for traction because the risk of avulsing the suture or vessel increases.

Steps of Hemorrhage Management

A methodical approach to intraoperative hemorrhage is critical to minimize patient injury. If an isolated vessel is clearly identified, then grasping it with a hemostat, vascular clamp, or fine forceps may allow ligation, electrosurgical coagulation, or vascular clip application.

In contrast, venous bleeding in the pelvis is typically from a venous plexus and rarely stems from a single vessel. Pelvic venous plexuses contain thin-walled veins. Accordingly, indiscriminate clamping, suturing, clipping, and electrosurgical coagulation may cause further laceration and bleeding. However, if other vulnerable structures have been retracted and protected, a few shallow stitches that incorporate such a bleeding area may be placed using fine absorbable suture.

If these initial efforts are unsuccessful and significant hemorrhage continues, the bleeding site is compressed with fingertip or sponge stick. Anesthesia staff should be informed of events to allow for additional monitoring. Resuscitative efforts with crystalloid or blood products are individualized depending on the degree of hemorrhage and other patient factors (Fluid Resuscitation and Blood Transfusion).

Adequate exposure of the bleeding site typically is needed to gain control of bleeding. The operative field should be assessed and increased as needed by extending a vertical incision cephalad, converting a Pfannenstiel to a Maylard incision, adding retractors, or converting a vaginal or laparoscopic approach to laparotomy. The site of bleeding should be evacuated of blood, and a second suctioning system may be indicated. Additional dissection of avascular planes around the bleeding site may improve isolation and ligation of a lacerated vessel. Furthermore, nearby vulnerable structures such as the bladder, ureter, or other vessels should be identified and protected.

After these steps, the surgeon may remove the tamponading finger to assess the location, amount, and character of bleeding and to formulate the most appropriate technique for control.

VESSEL LIGATION

Suture Ligature

Surgical knots have been used since the beginning of surgery to prevent blood loss during operative dissection and resection. Advantages to suture ligation include low cost and effectiveness over a broad range of vessel diameters. However, knot tying in general is time-consuming, limited in narrow spaces, and less commonly, associated with ligature slippage or breakage.

Small vessels may be ligated by a free-tie suture placed around the heel and tip of a vascular clamp and then secured with knots (see Fig. 40-27). Alternatively, surgeons often prefer to secure larger vascular pedicles with two separate sutures. The first ligature is a free tie placed around the toe and heel of a vascular clamp and tied. The second ligature is distal to the first and typically incorporates a bite through the tissue pedicle (see Fig. 40-30). Such *transfixion* of the ligature to the pedicle decreases the risk of it slipping off the pedicle's end. Importantly, placement of this second ligature distal to the first avoids hematoma formation if a vessel is pierced during transfixion.

Clips

Titanium clips seal vessels by direct compression. They are used more commonly during gynecologic oncology cases and offer the advantage of speed. However, clips are expensive, require surgical dissection of the vessel prior to application, and may dislodge from a vessel. Their use in routine gynecology is limited by these factors and surgeon preference.

Electrosurgical Seal

Electrical and ultrasound energy also may be used to seal vessels. Ultrasonic coagulating shears LaparoSonic Coagulation Shears, Ethicon, Pittscataway, NJ) and electrosurgical bipolar vessel sealing clamps (Ligasure, Valleylab, Boulder, CO) transfer energy that denatures vascular collagen and elastin and seal vessels up to 7 mm in diameter (Heniford, 2001). Thermal spread for both devices is comparable and averages 2.5 mm (Harold, 2003). These tools are particularly useful for laparoscopic surgeries, in which knot tying is time-consuming (Ding, 2005; Hagen, 2005; Hefni, 2005; Tamussino, 2005).

LOCAL HEMOSTATIC AGENTS

These topical products may be placed on bleeding sites where ligature or electrosurgical or ultrasonic vessel coagulation is not possible or has been ineffective. They are most effective in controlling low-pressure bleeding, such as from veins, capillaries, and

small arteries. Commercially available materials include those listed in Table 40-5. Some liquid hemostats deliver topical thrombin or thrombin and fibrinogen and thereby induce clot formation. Others transmit direct pressure against wound surfaces, entrap platelets, promote platelet aggregation, and serve as a scaffold on which clot can organize.

Table 40-5 Topical Hemostatic Agents

Type of Agent	Brand Name	Material
Oxidized, regenerated cellulose	Surgicel	Flat, fabric-like
Bovine collagen	Avitene, Instat	Powder, compressed sheet, or thin, flat sponge
Bovine thrombin	Thrombin-JMI	Liquid spray
Porcine gelatin	Surgifoam; Gelfoam	Putty or thin, flat sponge
Bovine thrombin and gelatin	FloSeal Matrix	Liquid
Human thrombin + fibrinogen	Crosseal; Tisseel	Needle tip or spray applicator

Although effective, these agents do have disadvantages. They should not be introduced intravascularly or used with cell salvage machines. Packing agents tightly into bony foramina should be avoided because these agents may swell, causing neurologic dysfunction or pressure necrosis. Moreover, they should not be placed within skin edges because they may retard edge reapproximation. Those composed of gelatin, collagen, or cellulose can serve as an infection nidus and thus, may not be appropriate in grossly infected tissue (C.R. Bard, 2007; Baxter, 2006; Pfizer, 2006).

Little data support the use of one agent over another. Selection typically is dictated by surgeon preference and operating room availability of an agent.

Specific Sites of Bleeding

Bleeding can develop during any type of gynecologic surgery. However, there are vascular complications that characteristically may complicate specific procedures, and surgeons may benefit from a familiarity with their management.

INFUNDIBULOPELVIC LIGAMENT

During or after ligation of this vascular pedicle, a lacerated ovarian vessel may retract into the retroperitoneum to create a hematoma. In most cases, isolation of the bleeding vessel is required to halt hematoma expansion.

Initially, the pelvic sidewall peritoneum lateral to the hematoma and the ureter is opened, and the incision is extended cephalad with fine scissors to the upper pole of the hematoma. Here, ovarian vessels are identified, and a closed Mixter right-angle clamp is placed under them. A free-tie pass then is threaded beneath and used to ligate these vessels. The hematoma then is evacuated to minimize infection risk.

In rare cases in which vascular or ureteral anatomy is unclear, an ovarian artery may require ligation as proximal as its aortic origin below the renal arteries (see Fig. 38-15) (Masterson, 1995).

PRESACRAL VENOUS PLEXUS

Sacrocolpopexy requires entry into the retroperitoneum and the presacral space (see Fig. 38-24). During entry, the presacral venous plexus can be injured during dissection or suturing. Vessels may retract into the vertebral bone, and problematic bleeding may result. Initially, injury to the plexus is managed with constant pressure over several minutes. As pressure is removed, an isolated vessel may be identified and sutured with fine absorbable suture. Extensive suturing, however, is discouraged because this can lead to additional vessel laceration and bleeding. Alternative methods of control have included the use of bone wax, insertion of a sterile thumbtack through the vessel and into the vertebral bone, and placement of hemostatic agents such as Floseal Hemostatic Matrix (Baxter, Deerfield, IL). In rare refractory cases, patient packing as described below may be required.

SPACE OF RETZIUS

This space is commonly entered during urogynecologic procedures and contains important vascular structures such as the venous plexus of Santorini, the obturator vessels, and the aberrant obturator vessel (see Fig. 38-25). (Baggish, 2001). Bleeding complications may develop, and approximately 2 percent of tension-free vaginal tape procedures are complicated by bleeding in this space (Kolle, 2005; Kuuva, 2002). In most instances, bleeding is controlled with pressure or suturing.

MAJOR PELVIC VESSELS

Fragile, high-volume veins within the pelvic sidewall include the internal, external, and common iliac veins and the inferior vena cava. These may be lacerated during tumor removal, endometriosis excision, or laparoscopic trocar placement. At times during lymphadenectomy, small veins that enter the anterior surface of the common iliac vein or the inferior vena cava may be avulsed.

In those comfortable with such vascular repair, a figure-of-eight or continuous running stitch may be placed with a 5-0 permanent monofilament suture (Gostout, 2002). Although gynecologic surgeons may attempt to repair these injuries, excessive delay in obtaining vascular surgery assistance often leads to greater blood loss (Oderich, 2004). Therefore, in many instances, pressure is applied, and a vascular surgeon is consulted for repair.

As discussed below, although internal iliac artery ligation does not lead to ischemia of central pelvic organs, injury to the external or common iliac arteries requires repair to maintain blood supply to the lower extremity. Consultation with a vascular surgeon may be indicated depending on the degree of laceration and surgeon skill. Such arterial tears may be closed with a continuous suture line using monofilament synthetic 5-0 suture (Tomacruz, 2001).

PARAMETRIAL AND PARAVAGINAL VESSELS

During obstetric and gynecologic surgery, laceration to vessels supplying the uterus and vagina, especially venous plexuses, may result in bleeding that cannot be easily identified and controlled following application of direct pressure, suturing, or a clip. In these extreme situations, ligation of the internal iliac artery, which is a main source of blood supply to the pelvis, may decrease pooling of blood and afford a better opportunity to find a bleeding source. Alternatively, if resources are available, pelvic artery embolization has been shown to be effective in controlling pelvic hemorrhage. Despite these techniques, in rare persistent situations, pelvic packing and termination of surgery may be indicated.

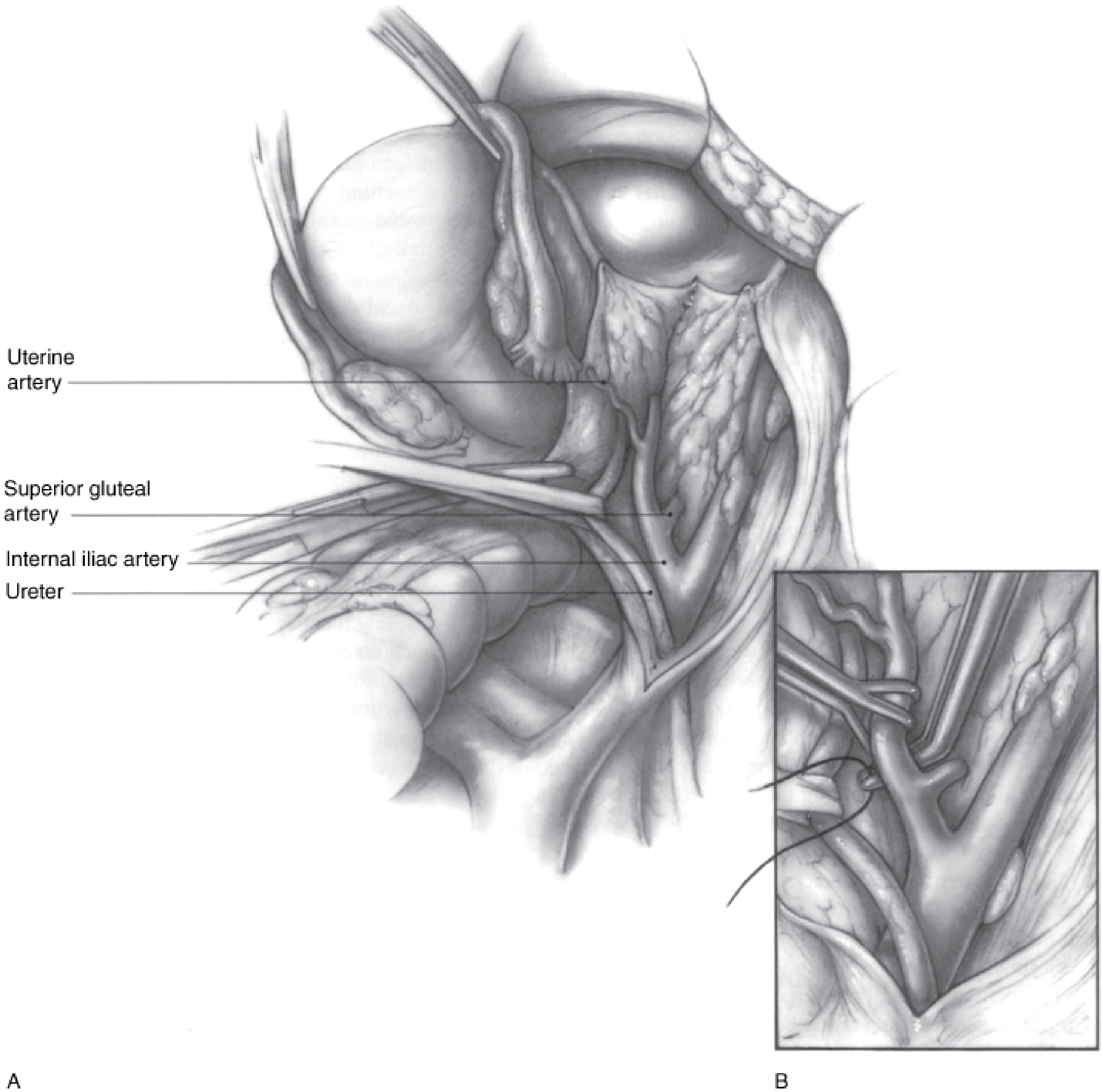
Internal Iliac (Hypogastric) Artery Ligation

The internal iliac artery, also known as the *hypogastric artery,* contains anterior and posterior divisions. Its anterior division supplies blood to central pelvic viscera (see Fig. 38-22). The female pelvis has extensive collateral circulation, and the internal iliac artery shares arterial anastomoses with branches of the aorta, external iliac artery, and femoral artery. For this reason, ligation of the internal iliac's anterior division can be performed without compromise to pelvic organ viability. Several studies have described normal postligation fertility in these women, and an investigation evaluating flow with color Doppler sonography showed recanalization of ligated arteries within an average of 5 months (Demirci, 2005; Khelifi, 2000; Nizard, 2003). Occlusion of the internal iliac artery decreases mean blood flow in branches distal to ligation by 48 percent, which in many cases slows hemorrhage sufficiently to allow identification of specific bleeding sites (Burchell, 1968).

To perform ligation, the round ligament is divided, and the pelvic sidewall peritoneum lateral to the infundibulopelvic ligament is incised cephalad. Identification of the internal iliac artery is essential because ligation of the common or external iliac arteries will have vascular consequences to the lower extremity.

Once the vessel is located, a Mixter right-angle clamp is placed under the vessel, and two free ties of no. 1 or 0 absorbable suture are passed beneath and then secured (Fig. 40-39). The artery is ligated but not transected (Gilstrap, 2000). Care is required in passing instruments beneath the artery because the thin-walled internal iliac vein is easily lacerated.

FIGURE 40-39



Internal iliac artery ligation. **A.** After opening the retroperitoneal space, the ureter is identified and retracted medially. **B.** The internal iliac artery is identified and gently elevated with a Babcock clamp. A Mixter right-angle clamp is placed beneath the artery to receive a free tie for ligation. *(From Gilstrap, 2002, with permission.)*

Pelvic Artery Embolization

As described in Chapter 9, Uterine Artery Embolization, embolization similar to that used to treat symptomatic leiomyomas can be used to occlude either the internal iliac artery or the uterine artery. This technique has been described in the management of hemorrhage in both gynecologic and obstetric cases (Kim, 2004; Pearl, 1992; Shim, 2006).

Pelvic Packing

In patients with persistent heavy bleeding despite attempts at control, pelvic packing with gauze and termination of the operation may be warranted. Rolls of gauze are packed against the bleeding site to provide constant local pressure. Typically, 24 to 48 hours later, if the patient is stable and bleeding appears to have stopped clinically, packing may be removed. Some surgeons recommend leaving one end of the gauze outside the wound. After administration of general anesthesia, packing is pulled slowly through a small opening left in the incision. Alternatively, entire gauze rolls may be packed into the abdomen and removed during a second laparotomy (Newton, 1988).

FLUID RESUSCITATION AND BLOOD TRANSFUSION

With acute hemorrhage, priorities include control of additional losses and replacement of sufficient intravascular volume for tissue perfusion and oxygenation. In hypoperfused areas, progressive failure of oxidative metabolism with lactate production leads to worsening systemic metabolic acidosis and eventual organ damage (Manning, 2004). To avoid these effects, resuscitation should begin with an assessment of the patient's clinical status, calculation of total blood volume, and estimation of blood loss.

Clinical Assessment

Total blood volume for an adult approximates 70 mL/kg, and thus a 50-kg woman's calculated blood volume is 3,500 mL. Of this volume, 15 percent can be lost by most patients with no changes in arterial pressure or heart rate. A 15-percent blood loss can be roughly calculated by multiplication of a patient's weight in kilograms by 10. Thus, for a 50-kg woman, a 15-percent loss approximates 500 mL.

With losses of 15 to 30 percent (500 to 1,000 mL for a 50-kg woman), tachycardia and narrowing of the pulse pressure are seen (Table 40-6). Peripheral vasoconstriction leads to pale, cool extremities and poor capillary refill. In unasthetized patients, there may be mild confusion or lethargy. In most women with normal preoperative hemoglobin levels, this amount of blood loss requires fluid volume replacement, but RBC transfusion typically is not required. Greater losses, however, lead to worsening perfusion, hypotension, and tachycardia. In these cases, blood transfusion in combination with fluid resuscitation typically is indicated (Murphy, 2001).

Table 40-6 Clinical Findings Associated with Increasing Severity of Hemorrhage

Hemorrhage Class	**Class I**	**Class II**	**Class III**	**Class IV**
Blood loss				
Percentage	<15	15â€“30	30â€“40	>40
Volume (mL)	750	800â€“1,500	1,500â€“2,000	>2,000
Blood pressure				
Systolic	Unchanged	Normal	Reduced	Very low
Diastolic	Unchanged	Raised	Reduced	Very low, unrecordable
Pulse (beats/min)	Slight tachycardia	100â€“120	120 (thready)	>120 (very thready)
Capillary refill	Normal	Slow (>2 s)	Slow (>2 s)	Undetectable
Respiratory rate	Normal	Normal	Tachypnea (>20/min)	Tachypnea (>20/min)
Urinary flow				
rate (mL/h)	>30	20â€“30	10â€“20	0â€“10

Extremities	Normal color	Pale	Pale	Pale and cold
Complexion	Normal	Pale	Pale	Ashen
Mental state	Alert	Anxious or aggressive	Anxious, aggressive, or drowsy	Drowsy, confused, or unconscious

From Baskett, 1990, with permission.

During surgery, blood collects in suction canisters and laparotomy sponges. Although calculations from these sources provide surgeons with an approximation, blood loss estimates typically are low, and inaccuracy increases as the length and extent of a procedure increases (Bose, 2006; Santoso, 2001). Additionally, a hematocrit may be measured to assess hemorrhage. However, hematocrit values typically lag true losses, and values may reflect only the degree of hemorrhage. For example, following a blood loss of 1,000 mL, hematocrit levels typically fall only 3 volumes percent in the first hour but usually reflect an 8 volume percent drop at 72 hours (Schwartz, 2006).

Fluid Resuscitation

If hypovolemia is identified, fluid resuscitation should begin with crystalloid solutions. If hypotension and tachycardia are present, rapid replacement is warranted, and 1 or 2 liters, as indicated, may be infused over several minutes. Normal saline and lactated Ringer solutions are the two crystalloids used commonly. For moderate hemorrhage, both perform equally well for fluid replacement (Healey, 1998).

Although crystalloids have an immediate effect to expand intravascular volume, a portion will extravasate into extracellular tissues. Thus, in the setting of hemorrhage, crystalloid volume should be administered in a 3:1 ratio of blood lost (Moore, 2004). Clinically, urine output of 30 mL or more per hour, heart rate less than 100 beats per minute, and systolic blood pressure greater than 90 mm Hg may be used as general indicators of volume improvement. If rapid crystalloid infusion fails to correct hypotension or tachycardia, then RBC transfusion usually is warranted.

In addition to crystalloid solutions, colloids also may be used for volume expansion. These fluids have higher molecular weights than crystalloids. As a result, a greater portion remains intravascularly and is not lost to extracellular extravasation. Despite this perceived advantage, studies comparing survival rates if crystalloids or colloids are administered find no superiority with colloids but greater expense (Roberts, 2004).

RBC Replacement

CLINICAL ASSESSMENT

The decision to administer RBCs is complex and must balance the risks of transfusion with needs for adequate tissue oxygenation. These needs will vary depending on the clinical setting, and an assessment should include hemoglobin level, vital signs, patient age, risks for further blood loss, and underlying medical conditions, especially cardiac disease. Accordingly, no specific hemoglobin threshold dictates when RBCs should be administered. However, consensus guidelines suggest that transfusion to a hemoglobin level above 10 g/dL is rarely indicated (Hill, 2002). If hemoglobin levels reach 6 g/dL, transfusion almost always is required (Madjdpour, 2006). Hemoglobin levels between 6 and 10 g/dL are more problematic, and patient factors and risk for continued hemorrhage should dictate therapy (American Society of Anesthesiologists, 1996).

TRANSFUSION

Compatibility Testing

When the possible need for transfusion is present, an order for a *type and screen* informs blood bank personnel that blood products may be required and initiates two tests to characterize a patient's RBCs. The first evaluation, termed *typing,* mixes commercially available standardized controls with a patient's blood sample to determine her ABO type and Rh phenotype. The second test, or *screen,* combines a patient's plasma sample with control RBCs that express clinically significant RBC antigens. If a patient has formed antibodies to any of these specific RBC surface antigens, then agglutination or hemolysis of the sample is seen.

Typing and screening require about 45 minutes to complete and are valid for 3 days in patients who do receive transfusion. In those who are not transfused, the validity is considerably longer and typically is determined by individual blood banks.

Alternatively, an order to *type and crossmatch* blood products alerts blood bank personnel to designate specific units of blood solely for one individual's use and to test blood in those specific units against the patient's for specific antigen reactions. If blood is needed immediately, however, and a full screen is not possible, then ABO type-specific blood or O-negative blood may be used.

Packed RBCs

Previously, whole-blood transfusion was used commonly to provide RBCs, coagulation factors, and plasma proteins, but this largely has been replaced by component therapy. Packed RBCs are the primary product used for most clinical situations, and concentrated RBC suspensions can be prepared by removing most of the supernatant plasma after centrifugation. One unit of packed RBCs contains the same red cell mass as 1 unit of whole blood at approximately half the volume and twice the hematocrit (70 to 80 percent). One unit of packed RBCs raises the hematocrit approximately 3 volume percent in an adult or increases the hemoglobin level of a 70-kg individual by 1 g/dL (Table 40-7) (Gorgas, 2004).

Table 40-7 Characteristics of Blood Components

Component	Volume, mL	Content	Clinical Response
PRBCs	180â€"200	RBCs	Increases Hb 10 g/L and Hct 3%
Platelets			Increases platelet count
Random-donor unit	50â€"70	5.5×10^{10}	5â€"10 $\times 10^{9}$ /L
Single-donor collection	200â€"400	3.0×10^{11}	>10 $\times 10^{9}$ /L within 1 h and >7.5 $\times 10^{9}$ /L within 24 h postransfusion
FFP	200â€"250	Coagulation factors, including fibrinogen	Increases coagulation factors 2%
Cryoprecipitate	10â€"15	Fibrinogen, factor VIII, vWF	Increases fibrinogen level 0.1 g/L

FFP = fresh-frozen plasma; Hct = hematocrit; Hb = hemoglobin; PRBCs = packed red blood cells; RBCs = red blood cells; vWF = von Willebrand factor.

Modified from Dzieczkowski, 2005, with permission.

COMPLICATIONS

Transfusion Reactions

Despite numerous tests for compatibility, adverse reactions to blood products can develop and may include an acute or delayed hemolytic transfusion reaction, febrile nonhemolytic transfusion reaction, or allergic reaction.

Acute Hemolytic Transfusion Reaction

Acute immune-mediated hemolysis usually involves destruction of transfused RBCs by patient antibodies and most commonly results from ABO incompatibility. Symptoms begin within minutes or hours of transfusion and may include chills, fever, urticaria, tachycardia, dyspnea, nausea and vomiting, hypotension, and chest and back pain. In addition, these reactions can lead to acute tubular necrosis or disseminated intravascular coagulopathy, and treatment is directed to these serious complications.

If acute hemolysis is suspected, transfusion should be halted immediately. A sample of the patient's blood should be sent with the remaining donor unit for evaluation in the blood bank. In patients with significant hemolysis, laboratory values will be altered. Specifically, serum haptoglobin levels will be lowered; serum lactate dehydrogenase and bilirubin levels will be increased; and

serum and urine hemoglobin levels will be elevated. Serum creatinine and electrolytes levels and coagulation studies additionally should be ordered.

To prevent renal toxicity, diuresis is prompted with intravenous crystalloids and administration of furosemide or mannitol. Alkalinizing of urine may prevent precipitation of hemoglobin within the renal tubules, and therefore, intravenous bicarbonate also may be given.

In contrast to acute hemolytic transfusion reaction, delayed hemolytic transfusion reactions may develop days or weeks later. Patients often lack acute symptoms, but lowered hemoglobin levels, fever, jaundice, and hemoglobinemia may be noted. Clinical intervention typically is not required in these cases.

Nonhemolytic Transfusion Reactions

Febrile nonhemolytic transfusion reaction is characterized by chills and a greater than 1Â°C rise in temperature and is the most common transfusion reaction. Blood transfusion typically is stopped to exclude a hemolytic reaction, and treatment is supportive. For patients with a previous history of febrile reaction, premedication with an antipyretic such as acetaminophen prior to transfusion is reasonable.

Urticaria alone may develop during transfusion and typically is not associated with serious sequelae. It is generally attributed to an allergic, antibody-mediated response to donor plasma proteins. The transfusion does not need to be stopped, and treatment with an antihistamine, such as diphenhydramine 50 mg orally or intramuscularly, usually is sufficient. Rarely, an anaphylactic reaction may complicate transfusion, and treatment follows that for classic anaphylaxis. (see Table 27-3).

Infection

Infectious complications associated with packed RBC transfusion are uncommon and are listed in Table 40-8. The risk for transmission of HIV and hepatitis B and C virus has diminished over the past decade, and bacterial contamination now stands as a greater infection risk. In addition, emerging infection concerns include transmission of West Nile virus, transfusion-transmitted virus (TTV), hepatitis G, Epstein-Barr virus, and Creutzfeld-Jakob disease (CJD) (Luban, 2005).

Table 40-8 Blood Product Transfusion Risks

Type of Risk/Complication	**Incidence**
Allergic reactions	1:2,000
Transfusion-related acute lung injury	1:4,000
ABO-incompatible transfusion	
Mistransfusion	1:14,000â€“1:18,000
Acute hemolytic reaction	1:6,000â€“1:33,000
Delayed hemolytic reaction	1:2,000â€“11,000
Infections	
Viral	
Hepatitis A	1:1 million
Hepatitis B	1:6,000â€“1:320,000
Hepatitis C	1:1.2 millionâ€“<1:13 million

Human cytomegalovirus (CMV)	1:10â€“1:30
Epstein-Barr virus (EBV)	1:200
Human immunodeficiency virus (HIV)	1:1.4 millionâ€“1:11 million
West Nile virus	1:3,000â€“1:5,000
Bacterial	
Yersinia enterocolitica, Serratia m, Pseudomonas aeruginosa, Enterobacter	1:200,000â€“1:4.8 million
Parasites	
Malaria	1:4 million
Prions	
Creutzfeldt-Jacob disease	Unknown
Immunomodulation/suppression	Unknown

From Strumper-Groves, 2006, with permission

Transfusion-Related Acute Lung Injury (TRALI)

This infrequent but serious complication of blood component therapy is similar clinically to acute respiratory distress syndrome (ARDS). Symptoms develop within 6 hours of transfusion and may include extreme respiratory distress, frothy sputum, hypotension, fever, and tachycardia. Noncardiogenic pulmonary edema with diffuse bilateral pulmonary infiltrates on chest radiography is characteristic (Toy, 2005). Treatment of TRALI is supportive and focuses on oxygenation and blood pressure support (Silliman, 2005; Swanson, 2006).

Platelets

For patients with moderate hemorrhage, RBC transfusion typically is sufficient, but for patients with severe hemorrhage, platelet transfusion also may be indicated. Platelets may be acquired from a single individual during plateletpheresis and are termed *single-donor platelets.* Alternatively, platelets may be derived from random units of whole blood and are referred to as *random-donor platelets.*

Fewer platelets are harvested from a unit of whole blood compared with the amount removed during donor plateletpheresis. Specifically, a single-donor platelet dose contains at least 3×10^{11} platelets in 250 to 300 mL of plasma, and this approximates the dose from six random-donor platelet concentrates. Each random-donor platelet concentrate contain 5.5×10^{10} platelets suspended in approximately 50 mL of plasma. Each concentrate transfused should raise the platelet count by 5 to 10×10^{9} /L, and the usual therapeutic dose is one platelet concentrate per 10 kg of body weight. Five to six concentrates provide a typical adult dose.

Donor plasma must be compatible with recipient erythrocytes because a few RBCs are invariably transfused along with the platelets. Thus, only platelets from D-negative donors should be given to D-negative recipients.

Surgical patients with bleeding usually require platelet transfusion if the platelet count is less than 50×10^{9} /L and rarely require therapy if it is greater than 100×10^{9} /L. With counts between 50 and 100×10^{9} /L, the decision to provide platelet transfusion is based on a patient's risk for additional significant bleeding (American Society of Anesthesiologists, 1996). In patients requiring a large transfusion, a standard 6-unit pack of platelets may be indicated for every 7.5 units of RBCs transfused (Ketchum, 2006).

Fresh-Frozen Plasma

This component is prepared from whole blood or by plasmapheresis and is stored frozen. Approximately 30 minutes are required for the frozen plasma to thaw. One unit contains all coagulation factors, including 2 to 5 mg/mL of fibrinogen in 250 mL of volume. Recommended dosing is 10 to 15 mL/kg.

Fresh-frozen plasma is used commonly as first-line hemostatic therapy in massive hemorrhage because it replaces multiple coagulation factors. It should be considered in a bleeding woman with a fibrinogen level below 1.0 g/L or with abnormal prothrombin and partial thromboplastin times (Cunningham, 2005).

Cryoprecipitate

This component is prepared from fresh-frozen plasma and contains fibrinogen, factor VIII, von Willebrand factor, factor XIII, and fibronectin. Cryoprecipitate was developed and used originally for treatment of hemophilia A and von Willebrand disease. However, specific factor concentrates are now available for these disorders, and thus the clinical indications for cryoprecipitate are limited.

Fresh-frozen plasma provides all coagulation factors and is favored in severe hemorrhage over cryoprecipitate. However, cryoprecipitate is an excellent source of fibrinogen and may be indicated if fibrinogen levels persist below 1.0 g/L despite administration of fresh-frozen plasma, such as in disseminated intravascular coagulopathy (DIC). The dose of cryoprecipitate is usually 2 mL/kg of body weight, and each unit contains about 15 mL volume. One unit should increase the fibrinogen level by 10 mg/dL (Erber, 2006).

ADJACENT ORGAN SURGICAL INJURY

Adequate operating exposure, meticulous surgical technique, and surgical experience are important factors in prevention of injury to surrounding organs during gynecologic surgery. However, these complications may arise especially in cases in which anatomy is distorted or the operating field is obscured by adhesions, blood, or tumor spread.

Ureter

These injuries are uncommon in benign gynecologic surgery, and incidences associated with all hysterectomy approaches range from 0.03 to 6.0 percent (Harkki-Siren, 1998; Ostrzenski, 2003; Visco, 2001). Rates of injury are increased with operations for pelvic organ prolapse and incontinence. Specifically, incidences of obstruction or injury as high as 11 percent during reconstructive surgery for pelvic organ prolapse surgery have been reported (Barber, 2000). Other risk factors include altered pelvic anatomy from malignancy, prior surgery, an enlarged uterus, or adhesions from endometriosis or prior pelvic inflammatory disease (PID).

Ureteral injury may include transection or obstruction following ligation or clamp crush. In addition, trauma to its outer sheath with subsequent disruption of ureteral blood supply can affect its viability. Although the ureter may be injured during a variety of procedures, several surgeries have critical points at which the ureter may be at greater risk. For example, clamping the uterine arteries or suturing the vaginal cuff during hysterectomy; ligating the infundibulopelvic ligament during adnexa removal; suturing the Douglas cul-de-sac or uterosacral ligaments during culdoplasty; and placing suspensory sutures during colposuspension all are associated with increased risk.

Ideally, injuries are recognized intraoperatively because those repaired at the time of initial surgery are associated with improved repair and lower patient morbidity (Neuman, 1991; Sakellariou, 2002). Injury may be visible or may be identified using cystoscopy. Detection with cystoscopy can be aided by intravenous administration of one 5-mL ampule of indigo carmine. This dye gives urine a blue color and improves identification of urine passage through ureteral orifices. Up to 90 percent of unsuspected ureteral injuries and 85 percent of unsuspected bladder injuries may be identified with the use of cystoscopy (Gilmour, 1999, 2006; Gustilo-Ashby, 2006). However, partial ureteral kinking can be missed with this procedure (Dandolu, 2003). Thus, cystoscopy cannot be relied on solely for the diagnosis of ureteral injury. Alternatively, intraoperative ureteral catheterization or intravenous urography may be used to isolate lesions.

Once noted, injuries may be corrected by stenting, end-to-end reanastomosis, or ureteroneocystostomy. These should be performed by surgeons skilled in these operation. Many injuries, however, are unsuspected and diagnosed following surgery. Women may complain of flank pain, fever, and costovertebral angle tenderness. Ureterovaginal fistula, ileus, urine peritonitis, and pyelonephritis may be noted.

To increase early detection, a broader use of intraoperative cystoscopy has been advocated (Ferro, 2003; Vakili, 2005). However, urinary tract injury during most gynecologic procedures is uncommon, and cystoscopy may be reserved for cases with greater risks for ureteral injury.

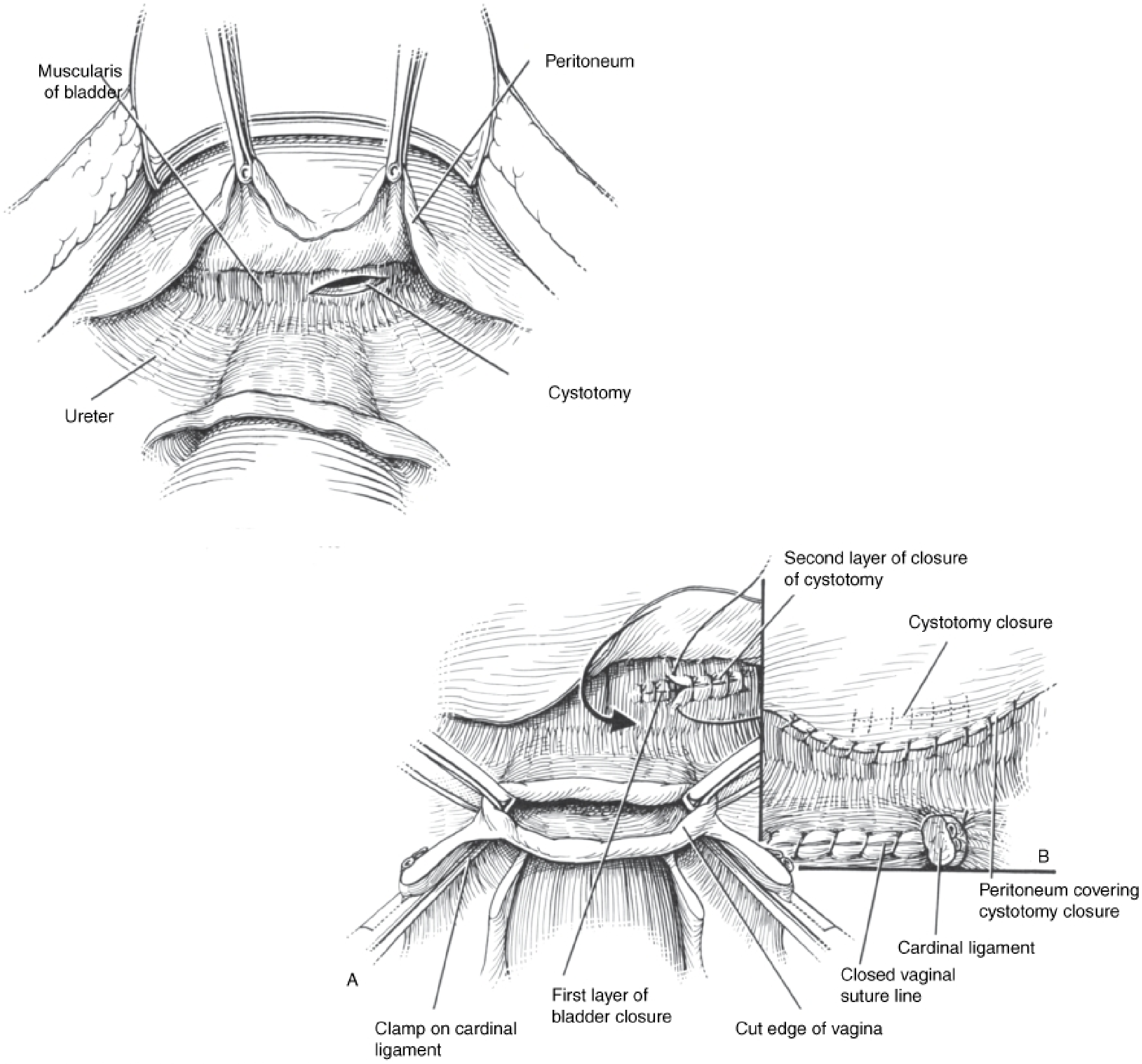
Bladder

Bladder injury is more frequent than ureteral damage during gynecologic surgery and may include perforation by sutures or laceration. It occurs most commonly during urogynecologic procedures and hysterectomy. Specifically, bladder injury complicates 1 to 2 percent of hysterectomies and is associated more commonly with a vaginal approach (Harris, 1997). Risk factors include prior pelvic reconstructive surgeries and prior cesarean delivery with scarring between the bladder and anterior uterus (Neumann, 2004; Rooney, 2005). Thus, depending on the prior procedure, the bladder may be at greater risk during: (1) initial abdominal entry when incising the anterior parietal peritoneum, (2) dissection within the space of Retzius, (3) dissection of the vaginal epithelium when performing anterior colporrhaphy, or (4) hysterectomy when dissecting the vesicouterine fold, entering the anterior vagina, or suturing the vaginal cuff.

Bladder injury is identified commonly at the time of surgery, and initially, a gush of clear fluid into the operating field may be seen. Laceration may be confirmed with instillation of sterile infant formula through a Foley catheter into the bladder. Leakage of opaque milk aids in identifying a laceration and delineating its borders. Additionally, cystoscopy may be indicated to further define bladder injury, exclude concurrent ureteral injury, or identify sutures placed through the bladder mucosa. If cystoscopy is performed, findings may be more clearly defined if indigo carmine is administered intravenously several minutes prior to the examination.

As with ureteral injury, repair at the primary surgery is preferred and lowers the risk of postoperative vesicovaginal fistula formation. Once ureteral patency is confirmed, the bladder may be closed with a two- or three-layer running closure using a 3-0 absorbable or delayed-absorbable suture (Fig. 40-40). The first layer inverts the mucosa into the bladder, and subsequent layers reapproximate bladder muscularis. Postoperative care requires continuous bladder drainage for 7 to 10 days.

FIGURE 40-40



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Cystotomy repair. The primary layer inverts the bladder mucosa with running or interrupted sutures of 3-0 delayedabsorbable or absorbable suture. Second and possibly a third layer approximate the bladder muscularis to reinforce the incision closure. *(From Lee, 1992, with permission.)*

Alternatively, if injury involves errant sutures placed through the bladder mucosa, sutures should be cut. Persistent sutures can lead to cystitis symptoms or stone formation or both.

Bowel

Injury to the bowel infrequently complicates gynecologic surgery, and rates in general lie below 1 percent (Harris, 1997; Makinen, 2001). Complications, however, may be more common in those with adhesions from prior surgery, infection, or endometriosis. Management of enterotomy varies considerably and typically is dictated by the size of injury, skill of the surgeon, and portion of the intestine entered. Short enterotomy wounds into the small intestine may be repaired with a layered closure using fine absorbable suture. During repair, rubber-shod clamps are placed across the intestinal lumen on either side of the wound to prevent spill of contents.

The large intestine carries a greater risk of contamination, but small enterotomies also may be managed as those of the small intestine. For most general gynecologists, larger incisions of either the small or large bowel, however, merit consultation with a general surgeon.

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41-1 MIDLINE VERTICAL INCISION

Vertical or transverse incisions both may be used to gain abdominal entry, and each offers particular advantages. Vertical incisions may be midline or paramedian, but of the two, the midline is chosen more often. This incision offers quick entry, minimal blood loss, superior access to the upper abdomen, generous operating room, and the flexibility for easy wound extension if greater space or access is needed.

Preoperative

PATIENT EVALUATION

Before any gynecologic procedure, all women with reproductive ability should be screened for concurrent pregnancy. Although many indicated gynecologic procedures may be performed during pregnancy, re-evaluation of the need and the approach to many operations are affected by concurrent pregnancy. Measurement of either urine or serum beta human chorionic gonadotropin (β-hCG) levels is typically used. In addition, to limit the possibility of an early, undetected luteal-phase conceptus, surgery may ideally be performed during the follicular phase, and an effective contraceptive method should be used until surgery.

As with pregnancy, cervical neoplasia may alter the need or approach to surgical correction of a gynecologic problem. For example, simple (Type 1) hysterectomy performed to treat a benign gynecologic condition will be inadequate treatment to cure most stages of cervical cancer (see Chap. 30, Treatment). Accordingly, women should have current Pap smear screening prior to surgery.

CONSENT

Despite surgical advantages, midline incisions are associated more frequently with greater postoperative pain and increased risk of incisional hernia than low transverse incisions. In addition, risk of bowel injury is present on abdominal entry, especially when extensive adhesions are present. Wound infection may follow any abdominal incision and is discussed in Chapter 3, Clinical Significance and Risks.

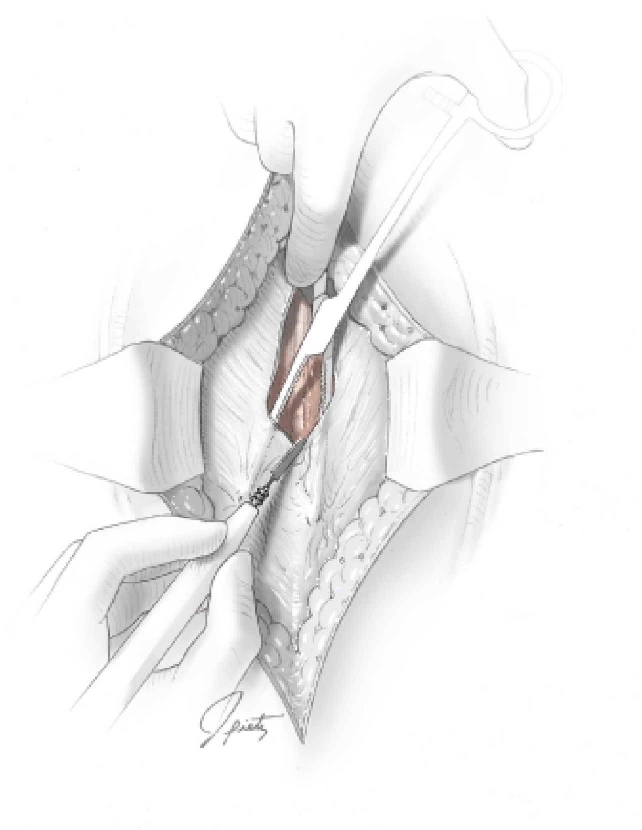
Intraoperative

Surgical Steps

1. **Anesthesia and Patient Positioning.** After administration of adequate regional or general anesthesia, the patient is positioned supine, a Foley catheter is placed, and sterile abdominal prep is completed.

2. **Skin and Subcutaneous Layer.** A midline vertical incision is made sharply beginning 2 to 3 cm above the symphysis pubis and extending cephalad to within 2 cm of the umbilicus (Fig. 41-1.1). In cases that require larger operating space or extensive access to the upper abdomen, the incision may arch around to the left of the umbilicus and continue cephalad as needed. The subcutaneous layers of Camper and Scarpa are incised to reach the fascial layer.

FIGURE 41-1.1



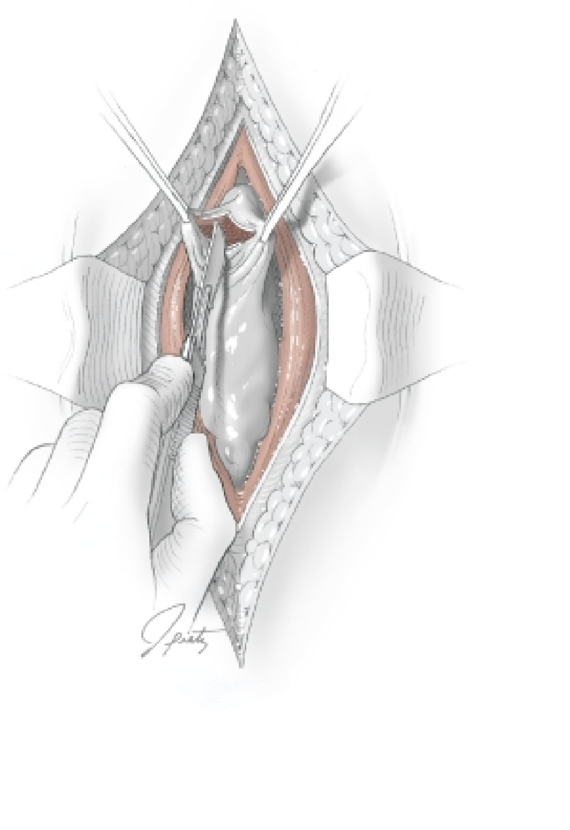
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Fascial incision.

3. **Fascia.** Tendinous fibers from the anterior abdominal wall muscles merge in the midline of the abdomen to form the linea alba (see Fig. 38-1). This fascia layer is entered sharply near the midpoint of the incision to avoid potential injury to the bladder inferiorly. This incision is extended cephalad and caudally to mirror the length of the skin incision. During this process, the linea alba may be elevated with fingertips or the ends of a pean clamp to minimize injury to tissues below (see Fig. 41-1.1).

4. **Peritoneum.** The peritoneum is identified between the bellies of the rectus abdominis muscle, grasped with two fine forceps or hemostats, and cut sharply. Similarly, this incision is extended cephalad and caudally (Fig. 41-1.2). Fingers are placed underneath and elevate the peritoneum to prevent bowel injury. As the incision is extended caudally, the bladder dome can be identified by the increasing vascularity and thickness of the peritoneum.

FIGURE 41-1.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Peritoneal incision.

5. **Operative Field.** Following access to the abdominal cavity, a self-retaining retractor commonly is placed to retract the muscles of the abdominal wall, the bowel, and omentum. Moist laparotomy sponges are placed caudally around the loops of intestines and gently directed cephalad. Upper blades of the retractor assist in holding these loops up and away from the pelvis and operating field. With the pelvic organs exposed, the planned abdominal surgery can proceed.

6. **Wound Closure.** The fascia is closed from one end to the other using a continuous running suture with a 0-gauge delayed-absorbable suture. If the subcutaneous layer measures less than 2 cm, then no closure is necessary. For deeper wounds, interrupted stitches of 4-0 delayed-absorbable suture are used to close this layer. The skin is closed with a subcuticular stitch using 4-0 delayed-absorbable suture or other suitable method.

Postoperative

For most gynecologic surgeries, recovery from the abdominal incision constitutes the greatest portion of postoperative healing. Midline incisions lead to significant pain with ambulation, coughing, and deep breathing. As a result, women undergoing laparotomy are at greater risk of postoperative thrombotic and pulmonary complications. For this reason, prevention of these complications is warranted (see Chap. 39). In addition, return of normal bowel function is commonly slowed, and signs of ileus should be monitored (see Chap. 39, Resumption of Bowel Function).

41-2 PFANNENSTIEL INCISION

The Pfannenstiel, Cherney, and Maylard incisions are transverse abdominal incisions used for gynecologic procedures. Of these, the Pfannenstiel incision is the most commonly used incision for laparotomy in the United States. As discussed in Chapter 38, because the incision follows Langer lines of skin tension, excellent cosmetic results can be achieved. Additionally, decreased rates of postoperative pain, fascial wound dehiscence, and incisional hernia are noted.

Use of the Pfannenstiel incision, however, is often discouraged for cases in which a large operating space is essential or in which access to the upper abdomen may be needed. Moreover, because of the layers created by incision of the internal and external oblique aponeuroses, purulent fluid could collect between these. Therefore, most cases involving abscess or peritonitis require a midline incision.

Preoperative

CONSENT

General risks associated with transverse laparotomy incisions are similar to those for vertical incisions (see Section 41-1, Midline Vertical Incision). However, these incisions also carry risk of nerve injury to the iliohypogastric, ilioinguinal, and femoral nerves (see Chap. 40, Laparotomy). These injuries more commonly involve sensory function and typically are transient.

Intraoperative

Surgical Steps

1. **Anesthesia and Patient Positioning.** After administration of adequate regional or general anesthesia, the patient is positioned supine, a Foley catheter is placed, and sterile abdominal prep is completed.

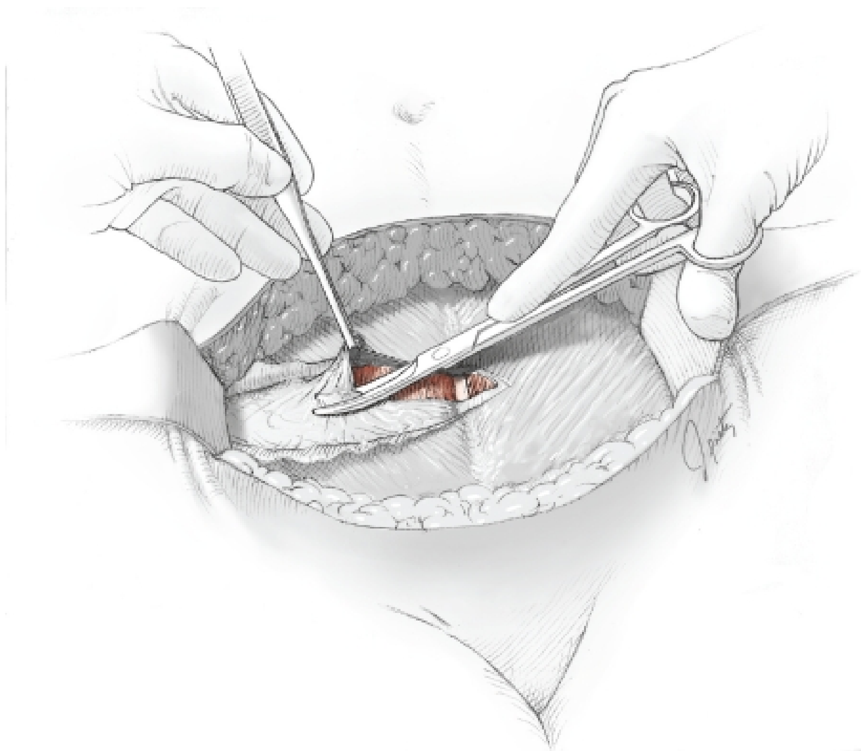
2. **Skin and Subcutaneous Layer.** About 2 to 3 cm above the symphysis pubis, an 8- to 10-cm transverse incision is made with its lateral margins arching slightly cephalad. The incision is extended deeply with electrosurgical blade through the subcutaneous layer until the anterior rectus sheath is reached. The superficial epigastric vessels lie in the subcutaneous layer within the path of this incision and may be severed during entry (see Fig. 38-2).

3. **Fascia.** The anterior rectus sheath then is incised transversely in the midline. At the level of the incision, the anterior rectus sheath typically is composed of two visible layers, the aponeuroses from the external oblique muscle and a fused layer containing aponeuroses of the internal oblique and transversus abdominis muscles Lateral extension of the anterior rectus sheath incision requires transverse incision of each layer individually (Fig. 41-2.1)

   The superior edge of the fascial incision is grasped with a Kocher clamp on each side of the midline. Traction is directed cephalad and slightly upward.

   In the area superior to the initial incision, the anterior rectus sheath then is separated bluntly or sharply from the underlying rectus muscle (Fig. 41-2.2). The fascia separates easily from the bellies of the rectus muscle but may be densely adhered along the midline. Several smaller perforating nerves and vessels traverse the space between the anterior rectus sheath and rectus muscle. Coagulation of these vessels, while avoiding injury to the nerves, should be undertaken during the separation. On completion of this dissection, a semicircular area with a radius of about 6 to 8 cm has been created. A similar separation is performed in the area inferior to the initial incision.

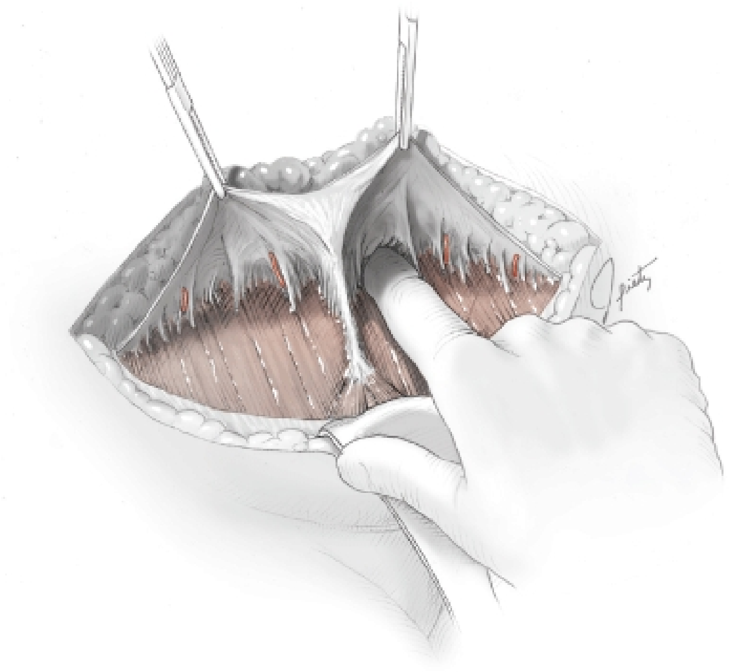
FIGURE 41-2.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Fascial incision.

FIGURE 41-2.2



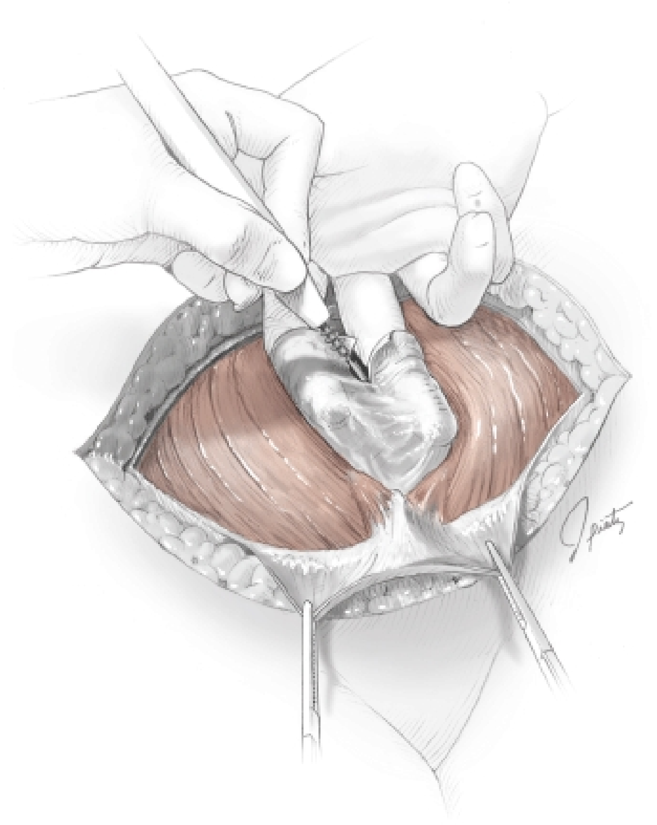
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Anterior rectus sheath separation.

4. **Rectus Abdominis Muscle.** The rectus abdominis muscle bellies then are separated along the midline either bluntly or sharply. The pyramidalis muscles, located superficial to the rectus muscle, usually require sharp division at the midline.

5. **Peritoneum.** On separation of the rectus muscle, the thin, filmy peritoneum is identified, grasped with two hemostats, and incised sharply. The peritoneal incision then is extended superiorly and inferiorly (Fig. 41-2.3). Once the abdominal cavity has been entered, the surgeon can proceed with the planned operation.

FIGURE 41-2.3

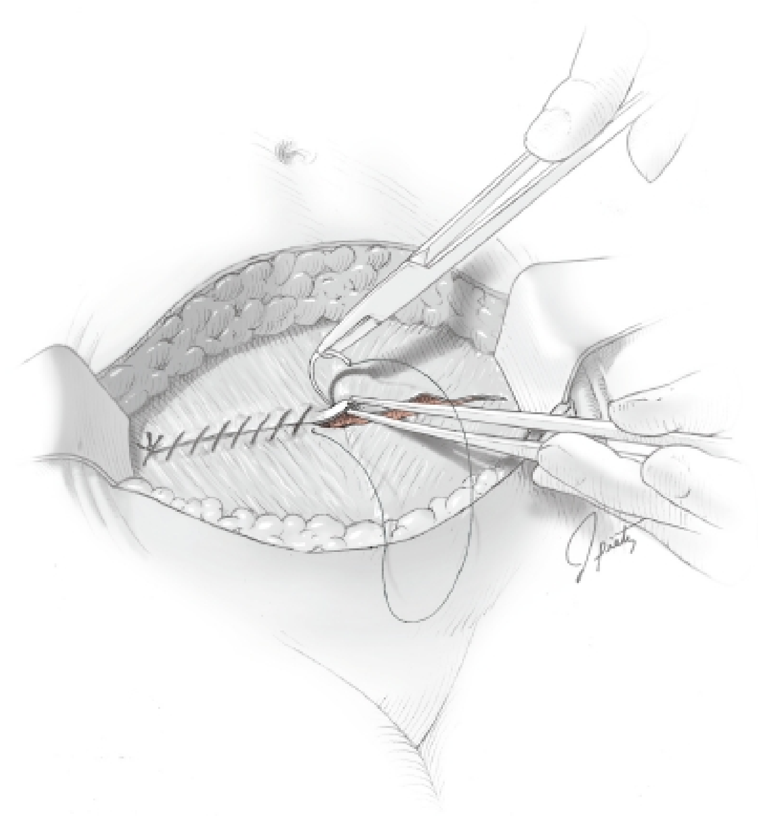


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Peritoneal incision.

6. **Wound Closure.** At completion of the intra-abdominal portion of surgery, closure of the incision begins. Closure of the visceral or parietal peritoneum is not encouraged (see Chap. 40, Wound Closure). The fascial layer is closed in a running suture using 0-gauge delayed-absorbable suture (Fig. 41-2.4). In patients with a greater than 2-cm subcutaneous layer, closure of this layer can decrease rates of wound infection and dehiscence. The skin may be closed with staples or a subcuticular stitch of 4-0 delayed-absorbable suture.

FIGURE 41-2.4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Fascial closure.

Postoperative

The postoperative course for low transverse incisions follows that described for midline incisions (see Section 41-1, Midline Vertical Incision).

41-3 CHERNEY INCISION

The Cherney incision is a tranverse abdominal incision that is similar to the Pfannenstiel incision in its early steps. After the anterior rectus sheath is opened, however, the tendons of the rectus and pyrimadalis muscles are transected 1 to 2 cm above their insertion into the symphysis pubis. These muscles then are lifted cephalad to provide access to the peritoneum.

This incision offers greater operating space as well as access to the space of Retzius and therefore may be a primary choice in cases when these requirements are anticipated. Additionally, Pfannenstiel incisions may be converted to Cherney incisions when an unexpected need for additional operating space arises.

Preoperative

Preparation and consent prior to a Cherney incision are similar to those for a Pfannenstiel incision (see Section 41-2, Pfannenstiel Incision).

Intraoperative

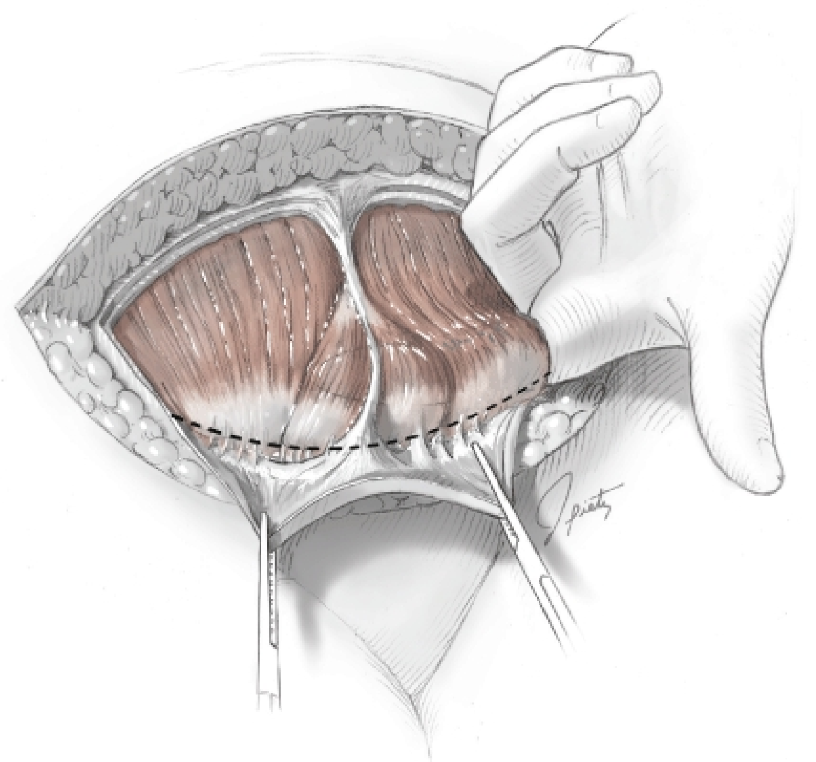
Surgical Steps

1. **Initial Steps.** The initial steps mirror those of the Pfannenstiel incision (see Section 41-2, Pfannenstiel Incision, steps 1 through 3). After lateral extension of the fascial incision, however, the techniques diverge.

2. **Fascia.** The fascial opening reveals the rectus abdominis muscles and the smaller, triangular-shaped pyrimadalis muscles, which lie more caudad and superficial. Cephalad to the symphysis pubis, fingers are insinuated underneath the rectus muscle tendons into the space of Retzius. This dissection begins laterally and extends toward the midline. Finger are insinuated in this manner to protect the underlying bladder from laceration during tendon transection.

   The tendons of both muscles then are transected 1 to 2 cm above the symphysis pubis (Fig. 41-3.1). The muscles are lifted cephalad. The peritoneum is grasped with two hemostats and is incised sharply. This incision is extended vertically. Once the abdominal cavity has been accessed, the planned surgery can proceed. If surgery is planned in the space of Retzius, and not intra-abdominally, then the peritoneum is not incised.

FIGURE 41-3.1

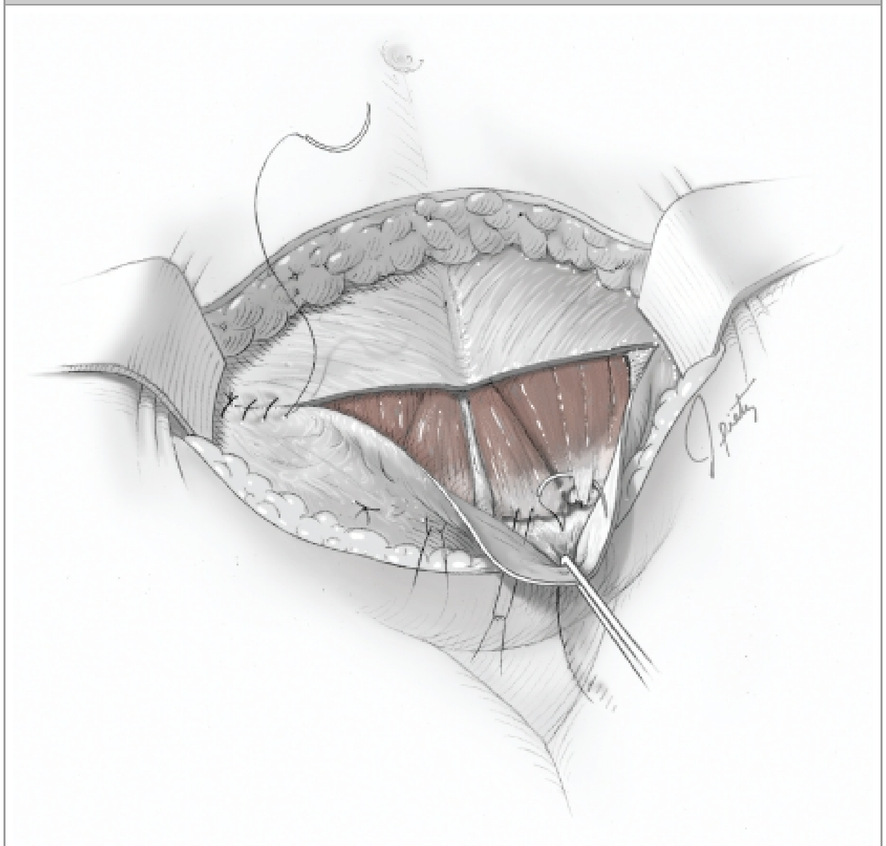


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Tendon transection.

3. **Wound Closure.** During wound closure, the cut ends of the rectus muscle tendons are affixed with interrupted sutures of 0-gauge delayed-absorbable sutures to the undersurface of the inferior fascia (Fig. 41-3.2). To avoid osteitis pubis or osteomyelitis, the tendons should not be affixed directly to the symphysis pubis. The fascia then is closed in a running suture using 0-gauge delayed-absorbable suture. The remaining incision closure follows that for the Pfannenstiel incision.

FIGURE 41-3.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Wound closure.

Postoperative

The postoperative course for low transverse incisions follows that described for midline incisions (see Section 41-1, Midline Vertical Incision).

41-4 MAYLARD INCISION

The Maylard incision differs mainly from the Pfannenstiel and Cherney incisions in that the bellies of the rectus abdominis muscle are transected. The main advantage to this incision is the larger operating space it affords. Therefore, it is selected often for cases in which greater access to the pelvis is needed. The Maylard incision is technically more difficult because it requires isolation and ligation of the inferior epigastric arteries. It also has been used infrequently because of concerns regarding greater postoperative pain, decreased abdominal wall strength, longer operating times, and increased febrile morbidity. Randomized studies, however, have not supported these concerns (see Chap. 40, Surgical Incisions).

Preoperative

Preparation and consent prior to a Cherney incision are similar to those for a Pfannenstiel incision (see Section 41-2, Pfannenstiel Incision).

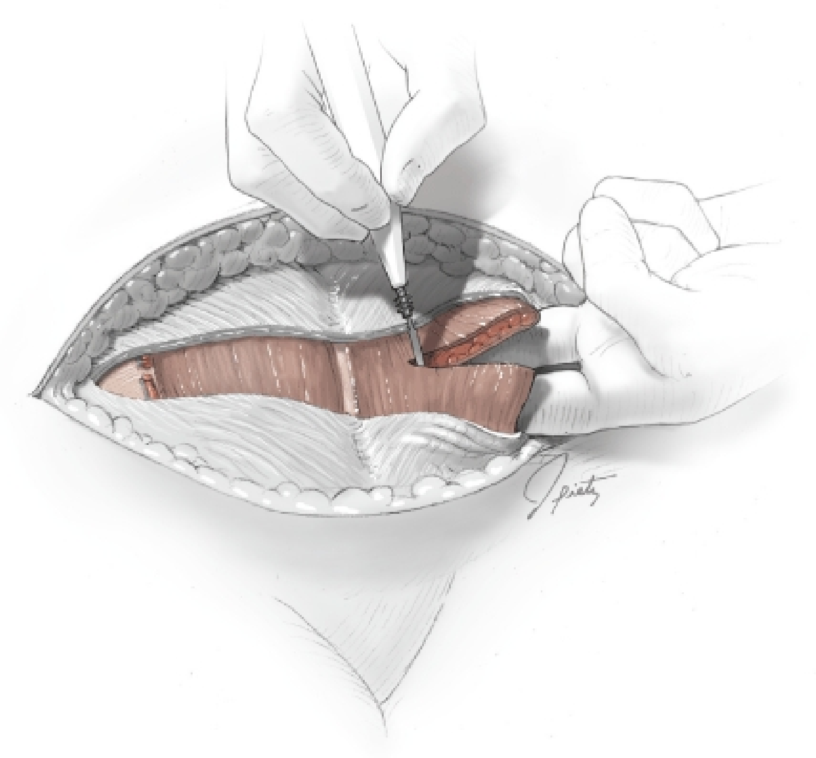
Intraoperative

Surgical Steps

1. **Initial Steps.** The initial steps mirror those of the Pfannenstiel incision (see Section 41-2, Pfannenstiel Incision, steps 1 through 3). After lateral extension of the fascial incision, however, the techniques diverge. The inferior epigastric artery and vein lie posterolateral to the bellies of the rectus abdominis muscle (see Figs. 38-2 and 38-3). Bilaterally, these vessels are identified, ligated, and transected. This step avoids their later laceration and hemorrhage when the rectus muscle is transected.

2. **Rectus Abdominis Muscle.** The rectus abdominis muscle is dissected bluntly away from the underlying peritoneum. The surgeon's fingers are placed behind the bellies of the rectus muscle, and this muscle then is transected using an electrosurgical blade (Fig. 41-4.1). Prior to transection, unlike the Pfannenstiel incision, the anterior rectus sheath should not be dissected away from the underlying rectus muscle. On the contrary, following muscle transection, to improve muscle reapproximation during incision closure, simple interrupted or mattress sutures using 0-gauge delayed-absorbable suture are placed 1 to 2 cm from the cut edge of the muscle and fascia to reinforce the anterior sheath attachment to the rectus muscle. This is performed on both the cephalad and caudad sections of the transected muscle (Fig. 41-4.2).

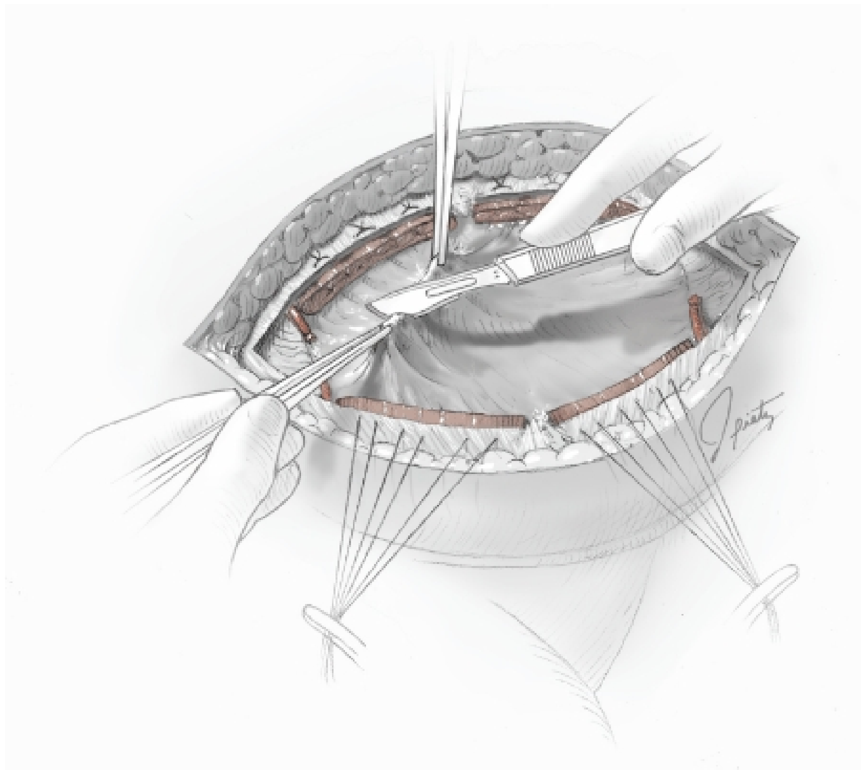
FIGURE 41-4.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Muscle transection.

FIGURE 41-4.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Suture placement and peritoneal incision.

3. **Peritoneum.** The peritoneum is grasped with two hemostats and incised sharply. Once created, the peritoneal incision is extended laterally. After obtaining access to the cavity, the planned abdominal surgery can proceed.

4. **Wound Closure.** At incision closure, the fascia is closed with a running suture using 0-gauge delayed-absorbable suture. Closing the fascia adequately reapproximates the transected muscles fibers, and therefore, the divided muscles bellies are not sutured directly together. The remaining incision closure follows that for the Pfannenstiel incision.

Postoperative

The postoperative course for low transverse incisions follows that described for midline incisions (see Section 41-1, Midline Vertical Incision).

41-5 HYMENECTOMY

Imperforate hymen results from failure of the hymen to canalize during the perinatal period. Most imperforate hymens are diagnosed after they have become symptomatic, usually during adolescence. Accordingly, the indications for hymenectomy may include complaints of amenorrhea, pain, abdominal mass, and urinary and defecation dysfunction. The diagnostic evaluation of these symptoms prior to surgery is discussed in Chapter 18, Description and Patient Presentation.

Less frequently, an asymptomatic imperforate hymen may be found during childhood. If there is no associated mucocoele, these lesions can be managed expectantly. Elective hymenectomy then can be performed during puberty but prior to menarche to avoid the development of hematometra or hematocolpos. At this developmental stage, the presence of estrogen can aid surgical repair and healing.

Preoperative

CONSENT

Hymenectomy is a simple gynecologic procedure, and most patients recover with no short- or long-term complications. Uncommonly, the hymeneal edges may re-epithelialize, and a repeat procedure may be required (Joki-Erkkila, 2003; Liang, 2003).

PATIENT PREPARATION

Conflicting opinions exist as to the need for prophylactic antibiotics, and little evidence exists to support either view (Adams-Hillard, 2005; Anania, 1994). If employed, intravenous antibiotics with polymicrobial coverage are given just prior to surgery.

Intraoperative

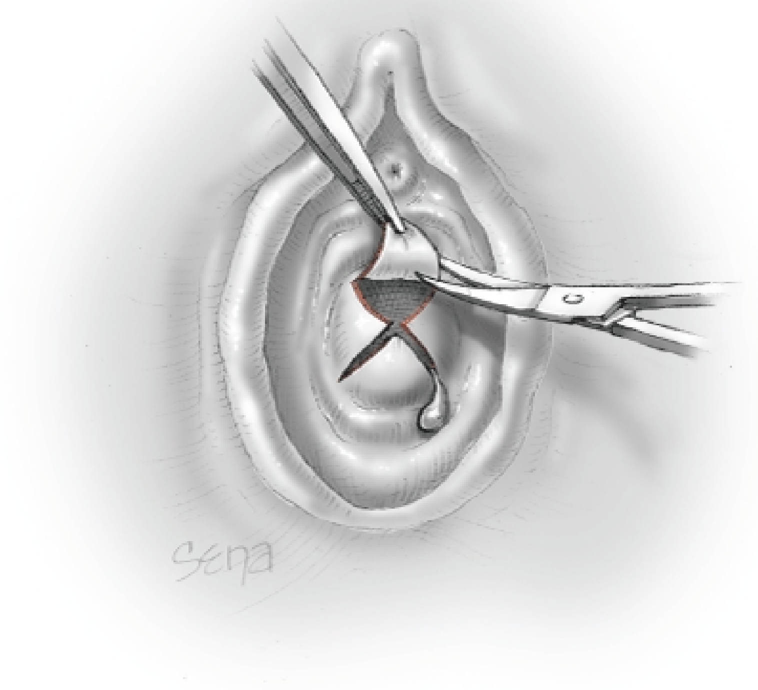
Surgical Steps

1. **Anethesia and Patient Positioning.** Hymenectomy typically is performed as a day-surgery procedure using general anesthesia. The patient is placed in the dorsal lithotomy position, the bladder is drained, and a sterile perineal prep is performed.

2. **Hymen Incision.** To avert injury to the urethra anteriorly and to the rectum posteriorly, the surgeon avoids creating pure vertical and horizontal incisions. Instead, a cruciate incision is made anteroposteriorly from 10 to 4 o'clock and from 2 to 8 o'clock into the hymeneal membrane (Fig. 41-5.1). Immediately, a stream of dark menstrual blood in the case of hematocolpos or mucoid fluid in the case of mucocolpos will follow.

   The hymeneal leaflets then are trimmed sharply from the hymeneal ring. The leaflets are not cut too close to the vaginal epithelium. This avoids increased scarring at the hymeneal ring.

FIGURE 41-5.1



Trimming hymenal leaflets.

3. **Irrigation.** The vagina is irrigated copiously using a sterile saline solution and bulb syringe.

4. **Suturing.** The cut edges of the leaflet bases then are oversewn with interrupted sutures using 3-0 or 4-0 delayed-absorbable suture, A ring of sutures is created (Fig. 41-5.2). A running interlocking suture is avoided to minimize circumferential narrowing of the introitus (Adams-Hillard, 2005).

   Intraoperative evaluation or manipulation of the upper vagina, cervix, and uterus is discourgaged. The walls of these organs may have been thinned by hematocolpos or hematometra and may be at greater risk for perforation.

FIGURE 41-5.2

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Suturing leaflet bases.

Postoperative

Following surgery, the patient may use oral as well as topical analgesics, such as 2-percent lidocaine jelly. Local wound care includes twice daily sitz baths. The patient is counseled that retained fluid may continue to drain from the uterus and vagina for several days following surgery. At 1 to 2 weeks following surgery, the introitus is inspected for patency and assessment of healing.

41-6 BARTHOLIN GLAND DUCT INCISION AND DRAINAGE

Bartholin gland duct cysts and abscesses are common vulvar masses encountered routinely in office gynecology (see Chap. 4, Bartholin Gland Duct Cyst and Abscess). Bartholin duct cysts typically measure 1 to 4 cm in diameter and are most commonly asymptomatic. Patients with larger cysts, however, may complain of vaginal pressure or dyspareunia. In contrast, patients with gland abscesses typically present with complaints of rapid unilateral vulvar enlargement and significant pain. Classically, a fluctuant mass is found either on the right or left side of the introitus, external to the hymenal ring, and at the lower aspects of the vulva.

Bartholin cysts or abscesses result from ductal opening obstruction followed by accumulation of mucus or pus within the duct. Bartholin gland duct abscesses are polymicrobial infections, and *Bacteroides* species, *Peptostreptoccus* species, *Escherichia coli,* and *Neisseria gonorrhoeae* are found commonly on culture of purulent drainage. Less typically, *Chlamydia trachomatis* may be involved (Bleker, 1990; Saul, 1988; Tanaka, 2005). Rarely, obstruction of this duct can develop following vaginal surgeries such as

posterior colporrhaphy or as a result of Bartholin gland cancer (Peters, 1998).

Incision and drainage (I&D) alone may give immediate but temporary relief. However, unless a new duct ostium is created, the incised edges following I&D will seal, and mucus or pus will re-accumulate. Therefore, I&D with subsequent steps to create a new ostium are surgical goals (Friedrich, 1983).

Permanent resolution of the cyst or abscess is common following either marsupialization or I&D with Word catheter placement. If obstruction re-occurs, however, repeating either of these procedures is preferable to gland excision for most patients. Bartholinectomy, as discussed next, carries significantly more morbidity than either of these procedures.

Preoperative

CONSENT

Repeated obstruction of the Bartholin gland duct following initial I&D is not uncommon during the weeks and months following drainage. Patients should be aware of the possible need to repeat the procedure should the duct obstruct again.

Intraoperative

INSTRUMENTS

As noted, the goal of Bartholin gland I&D is to empty the cystic cavity and create a new accessory epithelialized tract for gland drainage. For this purpose, a Word catheter (Milex Products, Inc., Chicago, IL) is used. Named after Dr. Buford Word, this catheter appears similar to a small, no. 10 French Foley catheter (Word, 1964). Word catheters are constructed of a 1-in latex tube stem that has an inflatable balloon at one end and a saline-injection hub at the other (Fig. 41-6.1)

FIGURE 41-6.1

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Word catheter. (Courtesy of J. Steven Willard.)

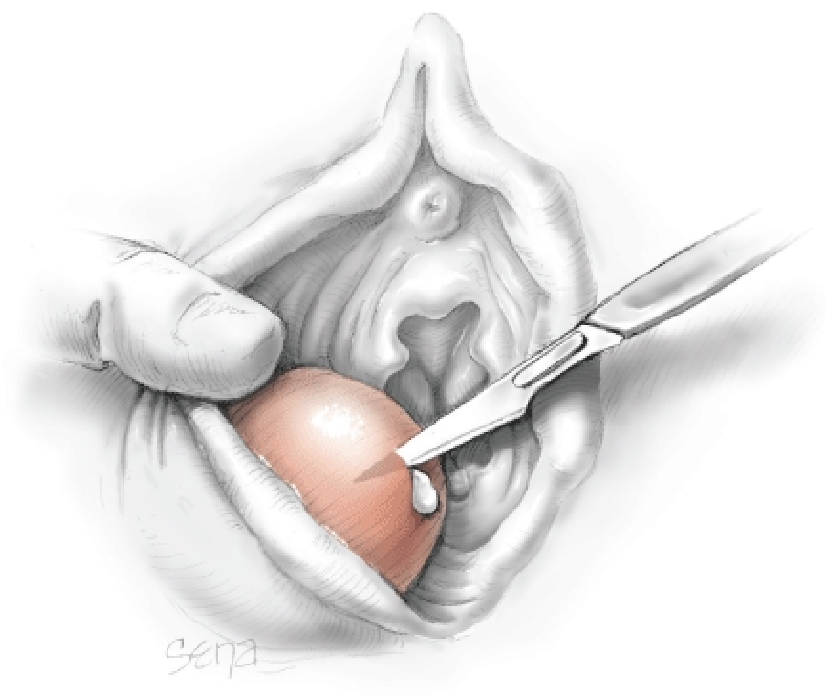
Surgical Steps

1. **Analgesia and Patient Positioning.** Most procedures are performed as an outpatient procedure in the office or emergency room. The patient is placed in the dorsal lithotomy position, and the wound is cleaned with a povidone-iodine solution (Betadine, Purdue Frederick Company, Norwalk, CT) or other suitable antiseptic agent. Local analgesia is sufficient for most cases and can be obtained by infiltrating the skin overlying the planned incision with an aqueous 1-percent lidocaine solution.

2. **Drainage.** A 1-cm incision is made using a scalpel with a no. 11 blade to pierce the skin and underlying cyst or abscess (Fig. 41-6.2). The incision should be made along the inner surface of the cyst or abscess and placed outside and parallel to the hymen at 5 or 7 o'clock on the surface of the vulva. This position mimics the normal anatomy of the gland duct opening and avoids creation of a fistulous tract to the outer surface of the labia majorum (see Fig. 38-27) (Hill, 1998). Cultures for *N gonorrhoeae* and *C trachomatis* can be obtained from spontaneously extruded pus. Mucus drained from a Bartholin cyst need not be cultured.

   The tip of a small hemostat is placed within the drained cavity, and the tips are opened and closed to lyse adhesions and open loculations of pus or mucus within the cavity.

FIGURE 41-6.2



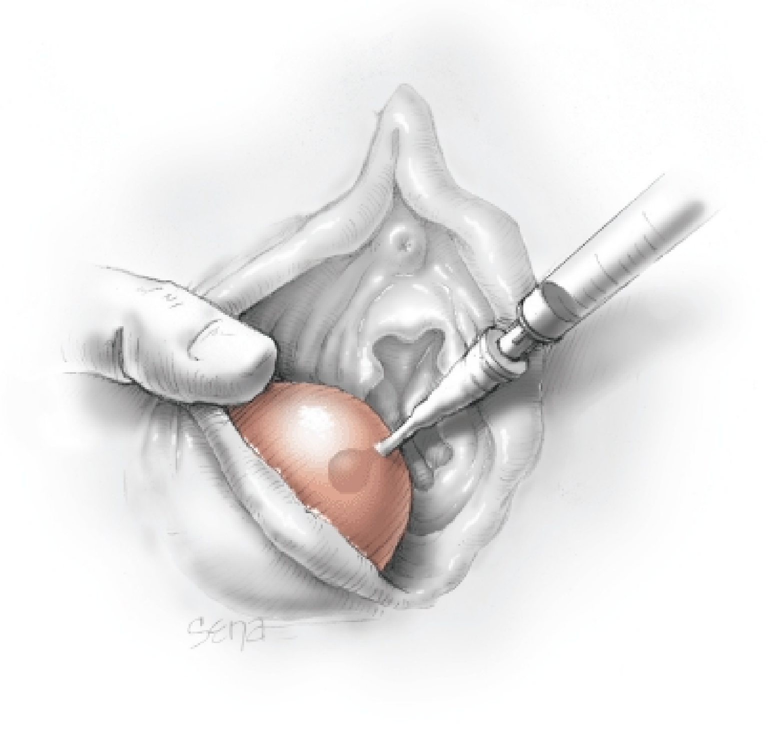
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Abscess or cyst incision.

3. **Word Catheter Placement.** The tip of a deflated Word catheter is placed within the empty cyst cavity. A syringe is used to inject 2 to 3 mL of sterile saline through the port of the catheter to inflate the catheter's balloon. The balloon is inflated to reach a diameter that will prohibit the catheter from falling out of the incision (Fig. 41-6.3).

   The hub of the Word catheter then can be tucked inside the vagina to prevent it from being dislodged by traction from perineal movement.

FIGURE 41-6.3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Word catheter in place.

Postoperative

Abscesses typically are surrounded by significant cellulitis, and in such cases, antibiotics are warranted. Antibiotics should be broad spectrum to treat a polymicrobial infection with aerobes and anaerobes (Omole, 2003).

Patients are encouraged to soak in warm tub baths twice daily. Coitus should be avoided for patient comfort and to prevent Word catheter removal. Ideally, the catheter is left in place for 4 to 6 weeks. Often, however, a catheter will be dislodged before this time. There is no need to try and replace the catheter if displaced, and attempts to reinsert it typically are not possible due to cavity closure.

41-7 MARSUPIALIZATION

High recurrence rates follow simple incision and drainage (I&D) of a Bartholin duct cyst or abscess. As noted earlier, a new duct ostium must be created to prevent the incised edges from adhering and allowing mucus or pus to re-accumulate. For this reason, marsupialization was developed as a means to create a new accessory tract for gland drainage (Jacobson, 1950; Matthews, 1966).

With introduction of the Word catheter, however, use of marsupialization has declined. Word catheter placement following I&D offers several advantages over marsupialization, and recurrence rates are equal (Blakely, 1966; Jacobson, 1960). Marsupialization requires a greater degree of analgesia, a larger incision, placement of sutures, and longer procedure time.

Preoperative

CONSENT

The consent for marsupialization mirrors that for Bartholin gland I&D. Accordingly, patients should be aware of the risk for repeated obstruction of the Bartholin gland duct following marsupialization. Patients should be aware of the possible need to repeat the procedure if ductal obstruction recurs.

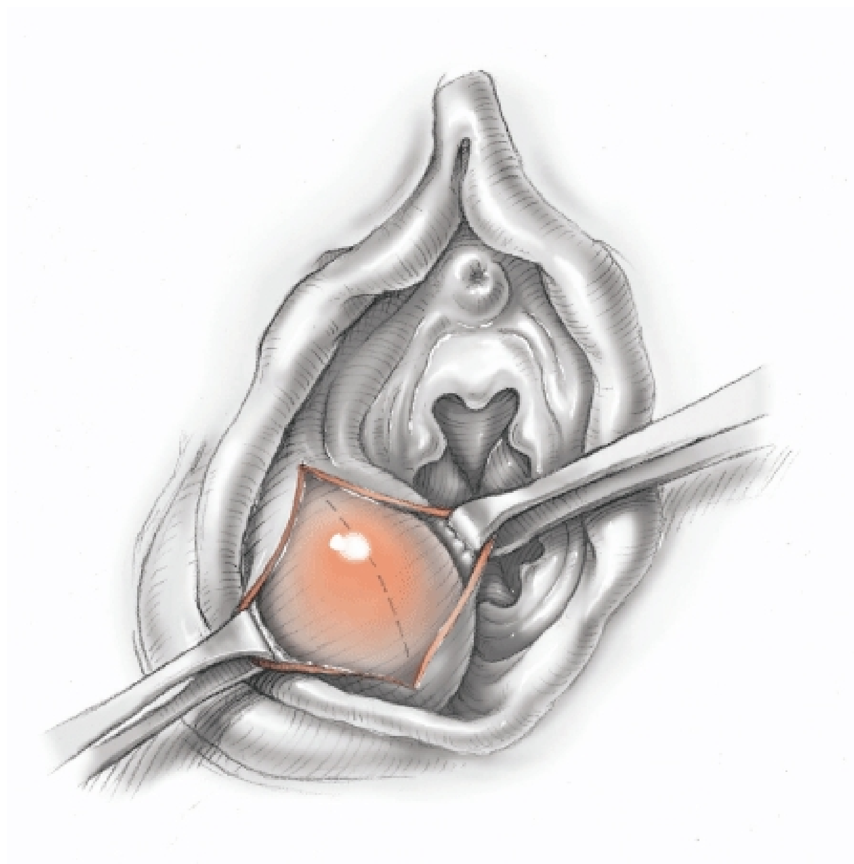
Intraoperative

Surgical Steps

1. **Anesthesia and Patient Positioning.** Marsupialization is an outpatient procedure typically performed in an operating suite using a unilateral pudendal nerve block or general anesthesia. Some authors, however, have described performance of the procedure in an emergency room setting (Downs, 1989). The patient is placed in the dorsal lithotomy position, and the vagina and vulva are surgically prepared.

2. **Skin Incision.** A vertical incision measuring 2 to 3 cm is created using a scalpel with either a no. 10 or no. 15 blade. The incision is made on the vestibule near the medial edge of the labia minora and approximately 1 cm lateral and parallel to the hymenal ring (Fig. 41-7.1). Care is taken to incise the skin but not to puncture the underlying cyst wall.

FIGURE 41-7.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Skin incision.

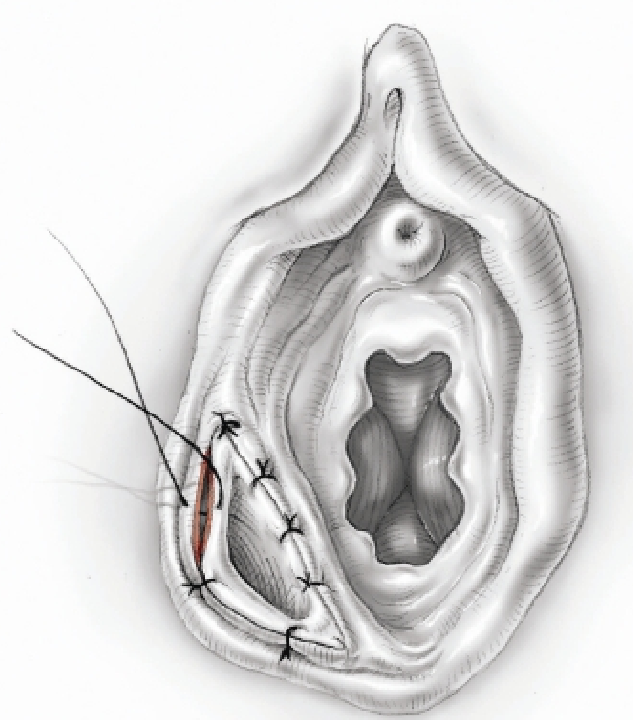
3. **Cyst Incision.** The cyst wall then is incised with a scalpel, and the incision is extended with scissors. Allis clamps then are

placed on the superior, inferior, right, and left lateral edges. Each clamp should grasp and contain the skin and cyst wall edges. These clamps then are fanned out.

The tip of a small hemostat is placed within the drained cavity, and the tips are opened and closed to lyse adhesions and open loculations within it. The cavity is rinsed with sterile saline, and suction is used to remove remaining saline and blood prior to wound closure.

4. **Wound Closure.** The edge of the cyst wall is sutured to its adjacent skin edge with interrupted sutures using 2-0 or 3-0 delayed-absorbable suture (Fig. 41-7.2).

FIGURE 41-7.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Cyst wall sutured open.

Postoperative

Cool packs during the first 24 hours following surgery can minimize pain, swelling, and hematoma formation. After this time, warm sitz baths, once or twice daily, are suggested for pain relief and wound hygiene.

Patients may be seen within the first week following surgery to ensure that ostium edges have not adhered to each other (Novak, 1978). Within 2 to 3 weeks, the wound shrinks to create a duct opening typically 5 mm or less in size. Recurrence rates following marsupialization are low, and Jacobson (1960) noted only 4 recurrences in his series of 152 patients.

41-8 BARTHOLINECTOMY

Most Bartholin gland duct cysts can be managed with incision and drainage (I&D) or with marsupialization. Symptomatic cysts, however, that recur repeatedly and refill following I&D or marsupialization are typical candidates for excision. Moreover, massive cysts or multilocular cysts may be best managed with excision.

Many authors have suggested excision of all Bartholin gland cysts in women older than age 40 to exclude cancer in the gland. However, a study by Visco and Del Priore (1996) suggests that the morbidity of gland excision may not be justified for this rare cancer. Instead, they recommend I&D of the cyst with biopsy of the cyst wall.

Preoperative

CONSENT

Because of the rich venous plexus of the vestibular bulb, significant bleeding can be encountered during bartholinectomy (see Fig. 38-27). In addition, gland excision can be associated with other morbidities, such postoperative wound cellulitis, hematoma formation, failure to remove the entire cyst wall with risk of recurrence, and pain or dyspareunia or both from postoperative scarring.

PATIENT PREPARATION

These cysts should be excised in the absence of concurrent abscess or surrounding cellulitis. Therefore, antibiotic administration typically is not required.

Intraoperative

Surgical Steps

1. **Analgesia and Patient Positioning.** Excision of most Bartholin cysts is performed as an outpatient procedure, in an operative suite, and under general anesthesia. The patient is placed in the dorsal lithotomy position, and a vaginal and perineal prep is performed.

2. **Skin Incision.** A gauze sponge held by a ring forceps is placed inside the vagina by an assistant, and pressure is directed outward along the posterior aspect of the cyst. This pushes the full extent of the cyst forward. The surgeon's fingers retract the labia minora laterally to expose the anterior surface of the cyst.

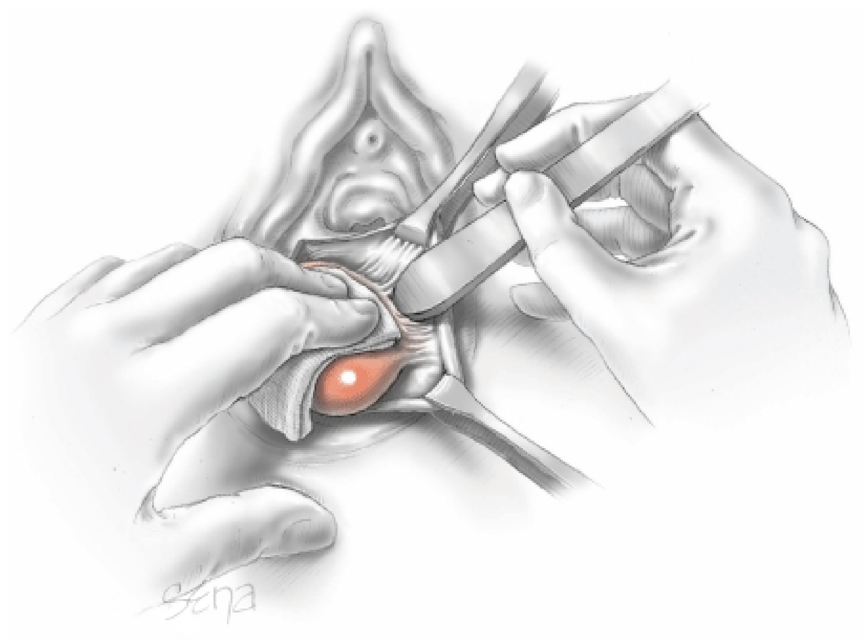
   A linear incision that extends the length of the cyst is made on the vestibule near the medial edge of the labia minora and approximately 1 cm lateral and parallel to the hymenal ring. Care is taken to incise the skin but not to puncture the underlying cyst wall. Allis clamps are placed on the medial skin edges and fanned out medially toward the contralateral labia.

3. **Cyst Dissection.** The greatest vascular structure supplying these cysts is located at the posterosuperior aspect of these cysts. For this reason, dissection should begin at the lower cyst pole and be directed superiorly.

   The inferomedial cyst wall is bluntly and sharply dissected away from the surrounding tissue (Fig. 41-8.1). Dissection planes should be kept close to the cyst wall to avoid bleeding from the venous plexus of the vestibular bulb and to avoid injury to the rectum. Because the lower-most pole of a Bartholin gland duct cyst may extend to lie adjacent to the rectum, the rectum can be entered accidentally during dissection. Placing a finger at times in the rectum can help to orient the surgeon to the spatial relationship between the two.

   Allis clamps then are placed on the lateral skin edges and fanned out laterally, and dissection is performed near the inferolateral cyst wall.

FIGURE 41-8.1

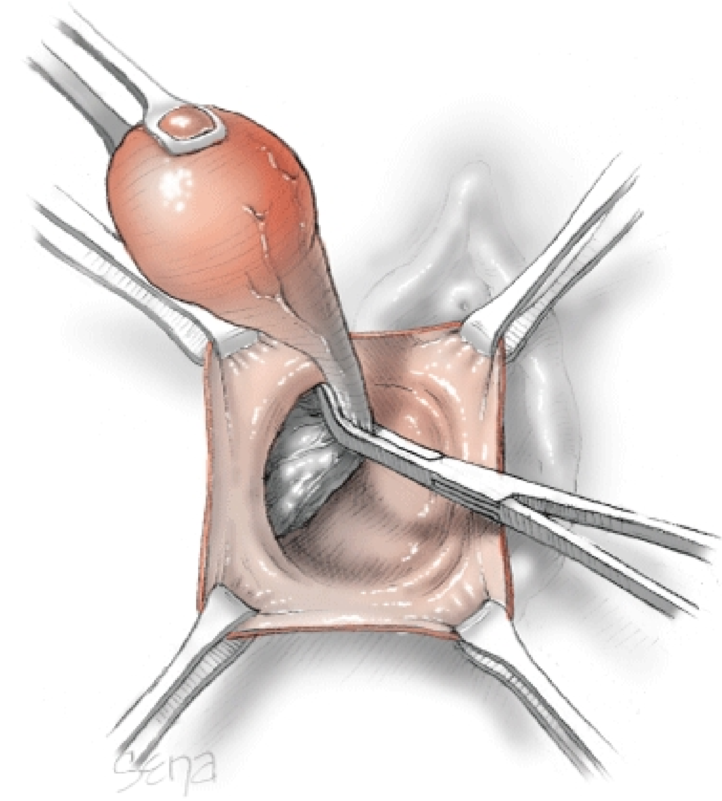


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Cyst dissection.

4. **Vessel Ligation.** As dissection is completed superiorly, the main vascular bundle to the cyst is identified and clamped with a hemostat. The bundle is cut and ligated with 3-0 delayed-absorbable or chromic suture (Fig. 41-8.2).

FIGURE 41-8.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Vessel ligation.

5. **Wound Closure.** The remaining cyst bed is closed in layers with running or interrupted sutures of 3-0 delayed-absorbable suture. Typically, two layers are required prior to skin closure, but in the case of large or vascular cyst beds, additional layers may be required. The skin is approximated with a running subcuticular suture of 4-0 delayed-absorbable suture.

Postoperative

Cool packs during the first 24 hours following surgery can minimize pain, swelling, and hematoma formation. After this time, warm sitz baths, once or twice daily are suggested for pain relief and wound hygiene.

41-9 VESTIBULECTOMY

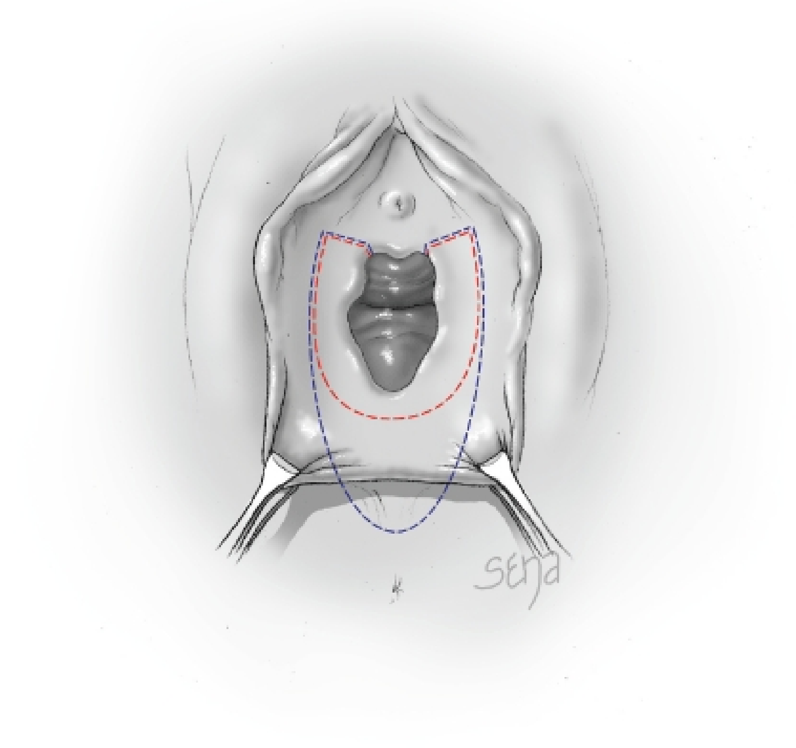
Anatomically, the vestibule extends along the inner labia minora from the clitoris to the fourchette (see Fig. 38-26). Additional borders include the hymenal ring and Hart line, which lies along the inner labia minora and demarcates the boundary between skin and mucosa. For some women, inflammation in this region can lead to vulvodynia and dyspareunia.

Most cases of vulvodynia are managed conservatively, but for refractory cases, three surgeries have been employedâ€”vestibuloplasty, vestibulectomy, and perineoplasty (see Chap. 4, Surgical Therapy) (Edwards, 2003). Vestibuloplasty involves denervation of the vestibule by incision, undermining, and then closure of the mucosa, but without excision of the painful epithelium. It generally has been found to be ineffective (Bornstein, 1995).

Alternatively, vestibulectomy incorporates excision of vestibular tissue (Fig. 41-9.1). Incisions extend from the periurethral area down to the superior edge of the perineum and include the fourchette. The incisions are carried laterally along Hart line and

medially should excise the hymen. In sum, mucous membrane, hymen, and minor vestibular glands are removed. Bartholin ducts are transected. Following excision, the vaginal mucosa is mobilized and pulled distally to cover the defect. In certain cases, a modified vestibulectomy is sufficient and only extends partially up the inner labia minora, well short of the periurethral area (Haefner, 2000; Lavy, 2005).

FIGURE 41-9.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Incisions for vestibulectomy *(red)* and perineoplasty *(blue)* .

Perineoplasty is the most extensive of the three procedures and extends from just below the urethra to the perineal body, usually terminating above the anal orifice. Similarly, following tissue resection, the vaginal epithelium is advanced to cover the defect. Although used most commonly to treat vulvodynia, perineoplasty also may treat fourchette fissuring and its associated pain caused by lichen sclerosis (Kennedy, 2005; Rouzier, 2002).

Preoperative

PATIENT EVALUATION

The most important factor for surgical success in treating vulvar pain is identifying the proper candidate (see Chap. 4, Vulvodynia). For example, vaginismus coexists in approximately half of patients with vulvodynia and, when present, is associated with lower rates of postoperative pain relief (Goldstein, 2005).

Prior to administration of anesthesia, the patient should undergo testing with a cotton swab to outline the areas of pain. These areas are marked with permanent marker prior to surgery to delineate the extent of excision (Haefner, 2005). Importantly, all sensitive areas should be removed, even those adjacent to the urethra; otherwise, tender foci that should have been resected as part of the primary operation may remain (Bornstein, 1995).

CONSENT

Vestibulectomy and perineoplasty are effective in treating vulvodynia, and in 80 to 90 percent of patients, pain either improves or resolves (Bornstein, 1999; McCormack, 1999; Schneider, 2001). Complications are infrequent but may include bleeding, infection, wound separation, Bartholin duct cyst formation, anal sphincter weakness, vaginismus, and vaginal stenosis (Haefner, 2000).

Intraoperative

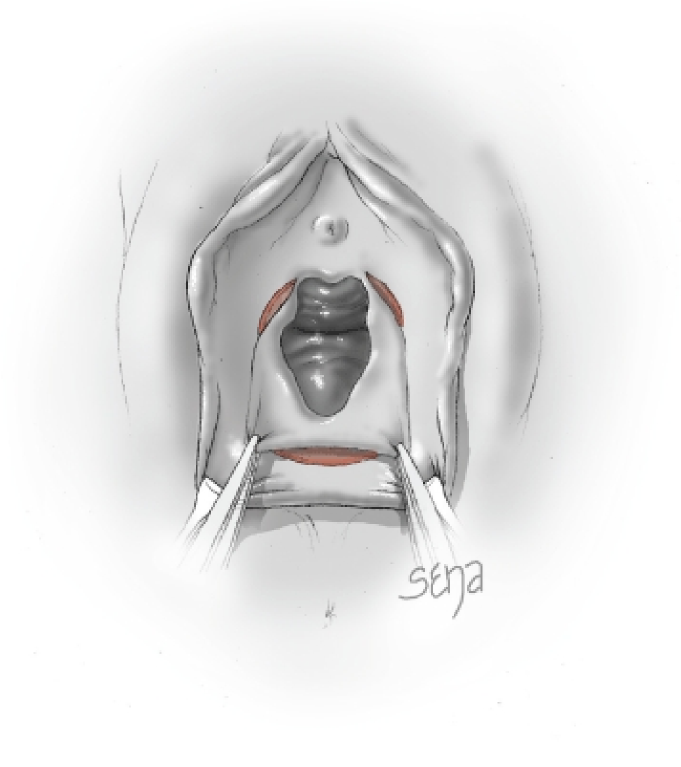
Surgical Steps

1. **Anesthesia and Patient Positioning.** Surgical marking of the sensitive areas to be excised precedes administration of anesthesia. In most cases, vestibulectomy is an outpatient procedure conducted using general or regional anesthesia. The patient is placed in dorsal lithotomy position, and the vulvovaginal area is surgically prepared.

2. **Surgical Excision.** The primary incision is made to a depth of 2 to 5 mm along the Hart line down to the perineum and proximal to the hymenal ring. The amount of tissue removed anteroposteriorly varies according to sensitivity mapping, but traditionally, it begins in the periurethral area and extends from the openings of the Skene ducts to the perineum. Accordingly, care should be taken to avoid injury to the urethra and alteration of the urethral angle.

3. **Vaginal Mucosal Advancement.** Following tissue excision, the cut edge of the vaginal mucosal edge is undermined 1 to 2 cm cephalad and then pulled distally to cover the defect (Fig. 41-9.2). To prevent hematoma and wound separation, hemostasis should be achieved prior to final suturing.

FIGURE 41-9.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Vaginal mucosal advancement.

4. **Wound Closure.** A deep closure layer using interrupted 3-0 delayed-absorbable sutures approximates the vaginal wall to its new site covering the vestibular defect. The superficial incision between the skin and vaginal epithelium is closed in an interrupted fashion with 4-0 delayed-absorbable suture.

Postoperative

Cool packs are used to relieve immediate discomfort, whereas sitz baths are initiated after the first 24 hours. Recovery typically is fast and without complications, and wound healing takes 4 to 8 weeks. Women usually meet with their surgeon during this time and are instructed to gradually resume intercourse 6 to 8 weeks following surgery (Bergeron, 2001).

41-10 LABIAL MINORA REDUCTION

When outstretched, most labia minora span 5 cm or less from their base to lateral edge. In some women, this span may be greater and may cause aesthetic dissatisfaction, discomfort with tight clothing, pain with exercise, and insertional dyspareunia. As a result, some elect to have their labia minora reduced surgically.

Goals of surgery include reduction in labial size and maintenance of normal vulvar anatomy. Early reductive procedures involved anteroposterior excision along the base of the labia and re-approximation of the surgical edges. Drawbacks to this approach include a marked color contrast at the suture line, where the dark outer labial minoral surface abutts the lighter inner surface. Moreover, the labial edge is often replaced by a stiff suture line. To reduce these affects, alternate techniques have incorporated labial wedging or Z- or W-plasty incisions (Alter, 1998; Giraldo, 2004; Maas, 2000).

Preoperative

CONSENT

Labial minora reductive surgery is a safe and effective means to remove excess labial tissues. As with any aesthetic procedure, women who are seeking cosmetic correction should have realistic expectations as to the final size, shape, and color of the labia. Wound complications such as hematoma, cellulitis, and incisional dehiscence are rare but should be discussed during counseling. Similarly, postoperative dyspareunia is uncommon but should be noted in the consenting process.

PATIENT PREPARATION

Antibiotics are not required for infection prevention, and no special preoperative patient preparation is needed.

Intraoperative

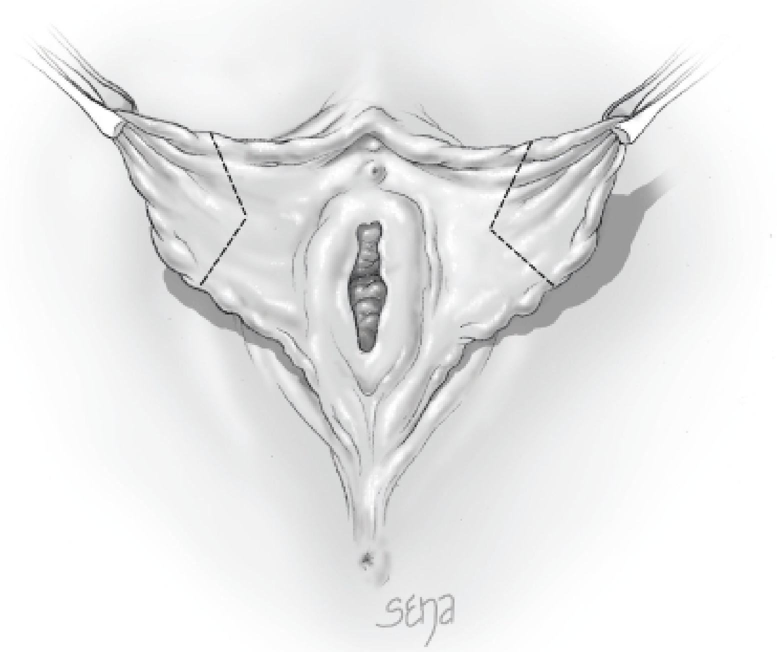
Surgical Steps

1. **Anesthesia and Patient Positioning.** Labial minora reduction may be performed as an outpatient procedure using general or regional anesthesia. After anesthesia has been delivered, the patient is placed in dorsal lithotomy position, and the vulva is surgically prepared.

2. **Labial Marking.** Excessive tissue removal should be avoided because aggressive reduction may lead to anteroposterior narrowing and discomfort during subsequent intercourse. For this reason, during surgical marking, the surgeon may chose to place several fingers in the vagina to distend its caliber. The labia minora then are outstretched laterally.

   The desired lateral span of the labia will vary among women, but most surgeons strive to create a span of 1 to 2 cm. Asymmetry between labia is common, and surgical marking helps to even this difference. With a surgical marker, the surgeon draws a V-shaped wedge on the ventral and dorsal surfaces of the labia minora demarcating the tissue for excision (Fig 41-10.1).

FIGURE 41-10.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Incision lines.

3. **Incision Infiltration.** The labia minora have a rich blood supply. To decrease bleeding, the incision may be infiltrated with a solution of 1-percent lidocaine and epinephrine in a 1:200,000 dilution.

4. **Wedge Excision.** The tissue wedge then is excised sharply. Hemostasis may be achieved using electrosurgical coagulation and is important in avoiding hematoma formation.

5. **Incision Closure.** The subcutaneous layers of the labia are re-approximated beginning proximally at the tip of the wedge. Interrupted sutures of 4-0 delayed-absorbable suture then are added outward toward the base to close the remainder of the wound. The skin is reapproximated with 5-0 delayed-absorbable suture in a running subcuticular or interrupted fashion.

Postoperative

Perineal hygiene is emphasized during the initial weeks following surgery. Exercise and intercourse may resume following wound healing.

41-11 TRANSVERSE VAGINAL SEPTUM EXCISION

Failure of the vaginal plate to regress completely during embryologic development can result in formation of transverse septums at various levels of the vagina (see Fig. 18-5). Some septums may have small perforations that allow prolonged menstrual blood

egress, whereas others may have no openings and lead to accumulations and distention in the upper reproductive tract. Some may be managed conservatively with observation, whereas those associated with pain, infertility, or hematometra require excision (see Chap. 18, Diagnosis and Treatment).

Preoperative

PATIENT SELECTION

Similar to the McIndoe procedure, this procedure is best performed in a mature adolescent or young adult rather than in children (see Section 41-12, McIndoe Procedure). First, production of estrogen following puberty can improve healing. Moreover, excision of these septums requires some degree of postoperative vaginal dilatation to avoid stricture, and regimen compliance may be limited in young girls. Unfortunately, not all cases can be delayed. Limitations include development of hematocolpos or hematometra. A fuller discussion of conservative management and surgical indications is found in Chapter 18, Diagnosis and Treatment.

CONSENT

Risks of transverse septum excision mirror those associated with the McIndoe procedure, except that skin grafting and its attendant risks usually are avoided unless the vaginal septum is long. Accordingly, vaginal stricture following excision is a significant risk. In their small series, Joki-ErkkilÃ¤ and Heinonen (2003) found that two of three adolescents required re-excision of scar tissue following initial septum removal.

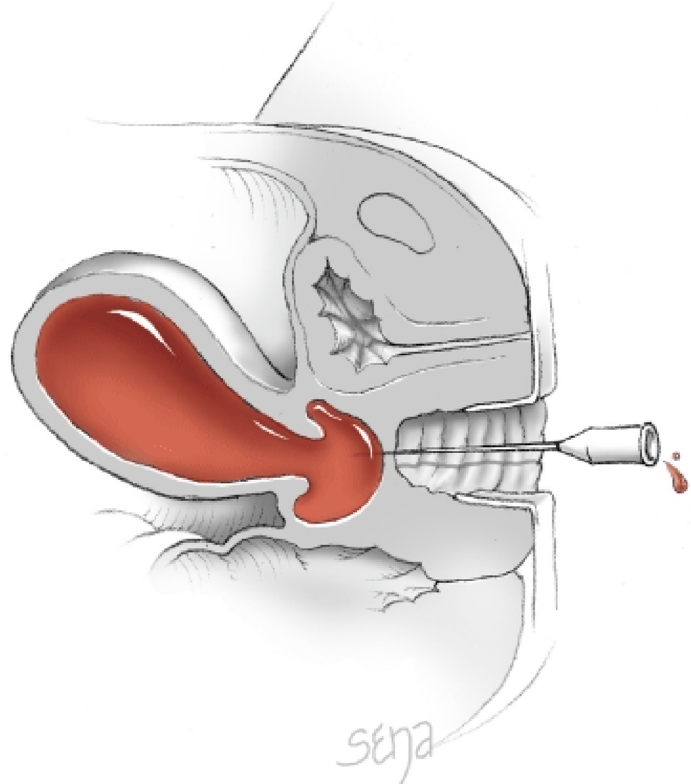
Intraoperative

Surgical Steps

1. **Anesthesia and Patient Positioning.** After administration of general anesthesia, a second-generation cephalosporin such as cefoxitin 2 g intravenously is given. The patient is placed in dorsal lithotomy position, and the perineum and vagina are surgically prepared. A Foley catheter serves as a guide to avoid urethral injury during septum excision.

2. **Incision.** Retractors are placed to reveal the upper extent of the vagina. With higher-level septums, diagnostic needle aspiration of the suspected hematocolpos can help to locate the upper vagina to determine the direction of dissection (Fig. 41-11.1). The vaginal vault is then incised transversely to avoid laceration of the urethra, bladder, or rectum (Fig. 41-11.2).

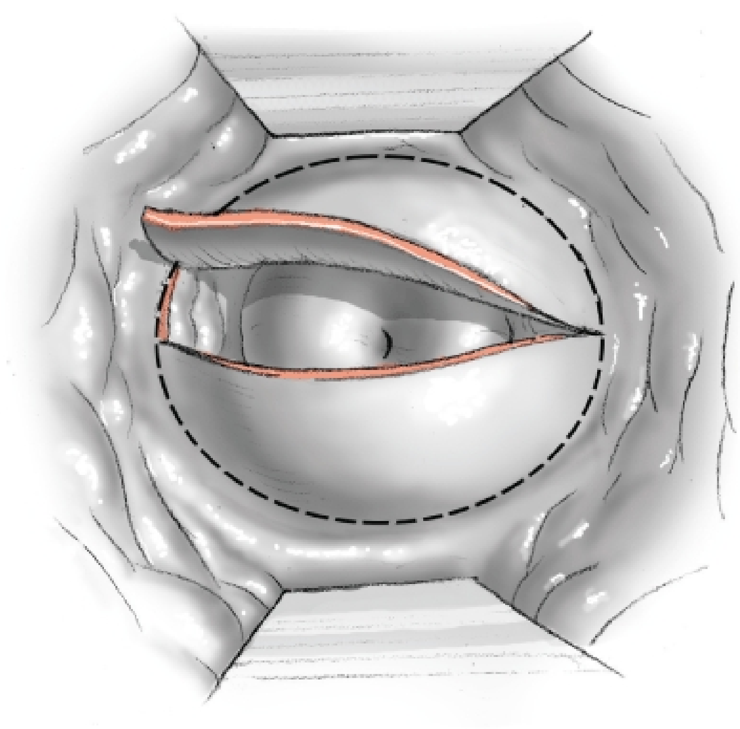
FIGURE 41-11.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Diagnostic needle aspiration to direct dissection.

FIGURE 41-11.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Septum incision.

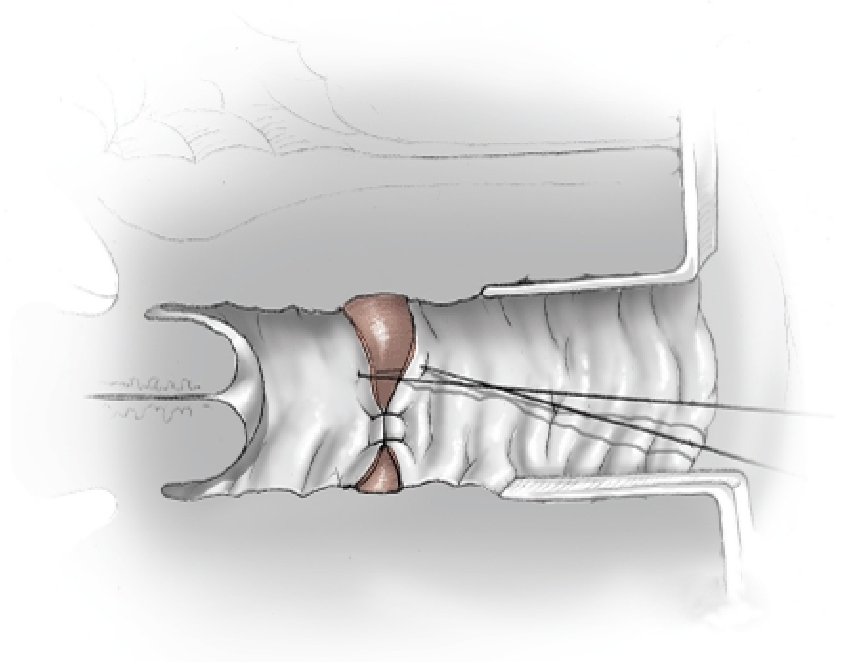
3. **Dissection.** Depending on its thickness, both blunt and sharp dissection may be required to transect the septum. Blunt probing of septal tissue to identify the upper vagina may be necessary to direct dissection. Similarly, the Foley catheter or a finger in the rectum may assist with orientation.

4. **Excision.** Once the septum is transected, the cervix is identified. The septum is excised widely to its base to minimize postoperative stricture.

5. **Wound Closure.** The vaginal mucosa is undermined, and the cephalad mucosal edge is sutured to the opposite caudad edge (Fig. 41-11.3). A circumferential ring of interrupted sutures thus is constructed using 2-0 delayed-absorbable suture. A soft stent, similar to that used in the McIndoe procedure, is placed into the vagina.

   If the vaginal septum is long and mucosal re-approximation is not possible, a skin graft can be taken and applied in a manner similar to the McIndoe procedure.

FIGURE 41-11.3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Vaginal mucosa reapproximation.

Postoperative

The Foley catheter may be removed on the first postoperative day. The remaining postoperative care mirrors that for the McIndoe procedure.

41-12 MCINDOE PROCEDURE

Creation of a functional vagina is the treatment goal for many women with congenital agenesis of the vagina. Although several surgical and nonsurgical approaches have been used, the McIndoe procedure is employed most commonly in the United States (see Chap. 18, Treatment). With this technique, a canal is formed between the urethra and urinary bladder anteriorly and the rectum posteriorly (McIndoe, 1938). A skin graft obtained from the patient's buttock, thigh, or inguinal regional then is wrapped around a soft mold and placed into the newly created vagina to allow epithelialization. Alternatively, other materials have been used to line the neovagina. These include amnionic membrane, cutaneous and myocutaneous flaps, buccal mucosa, and Interceed absorbable adhesion barrier (Ethicon, Somerville, NJ) (Ashworth, 1986; Lin, 2003; McCraw, 1976; Motoyama, 2003).

Preoperative

PATIENT SELECTION

Vaginal stricture can be a significant complication following the McIndoe procedure (Alessandrescu, 1996). Thus, adherence to a postoperative regimen of vaginal dilatation is mandatory. For this reason, surgery may be postponed until a patient has reached a level of maturity to comply (American College of Obstetricians and Gynecologists, 2002).

CONSENT

Prior to surgery, patients should be informed of overall success rates with this procedure. In a Mayo Clinic series of 225 patients, the McIndoe procedure provided a functional vagina to afford "satisfactory" intercourse in 85 percent of patients. In this review, the

cumulative complication rate was 10 percent and included vaginal stricture, pelvic organ prolapse, graft failure, postcoital bleeding, and fistulas involving either the bladder or rectum (Klingele, 2003). Additionally, complications at the skin graft harvest site involved cheloid formation, wound infection, and postoperative dysaesthesias.

PATIENT PREPARATION

Intravenous administration of a second-generation cephalosporin such as cefoxitin 2 g in a single preoperative dose is recommended. Bowel preparation is completed the evening prior to surgery (see Chap. 39, Gastrointestinal Bowel Preparation).

Intraoperative

INSTRUMENTS

Electrodermatome

The skin grafts used to line the neovagina are harvested from a donor site with the aid of an electrodermatome, which is able to shave grafts of varying size and depth. Both split- and full-thickness skin grafts have been used in the McIndoe procedure, and the electrodermatome settings are adjusted to shave the desired depth.

Vaginal Mold

Following graft harvesting and neovagina formation, a stent is needed to apply the graft to the vaginal walls and hold it in place. Both soft and rigid forms have been used. Rigid mold materials have included balsa wood, pyrex, plastic, and synthetic silicone-based materials (McIndoe, 1938; Ozek, 1999; Seccia, 2002; Yu, 2004). Unfortunately, rigid and semirigid stents have led to graft loss, fibrosis, contracture, and pressure-related bladder or rectal fistulas.

Use of soft stents has decreased the number of these complications. Inflatable rubber stents or condoms filled with foam rubber or other soft, compressible materials are examples (Adamson, 2004; Barutcu, 1998; Concannon, 1993). The vaginal graft produces abundant exudates, and poor drainage may lead to graft maceration, sloughing, and detachment. Accordingly, suction is attached to the soft stents to aid drainage of the neovagina (Yu, 2004).

Surgical Steps

1. **Anesthesia and Patient Positioning.** General anesthesia is administered, and the patient initially is positioned prone for skin graft harvesting from the buttock. Alternatively, skin may be obtained from the thigh, hip, or inguinal area. Goals of harvesting are to choose a location that has minimal hair growth and is cosmetically discreet. The assistance of a plastic surgeon may be enlisted for skin graft procurement.

2. **Skin Graft.** The surgeon first marks the outline of the wound on the skin of the donor site, enlarging it by 3 to 5 percent to allow for skin shrinkage immediately after excision. The surgeon uses the electrodermatome to remove a single strip of skin that is typically 0.018 in thick, 8 to 9 cm wide, and 18 to 20 cm long (Fig. 41-12.1). Alternatively, two smaller strips of 5 cm by 10 cm can be obtained from each buttock.

   Following excision, the graft is placed in a pan of sterile saline. The harvest sites on the buttocks are dressed with a Tegaderm dressing (3M, St. Paul, MN).

FIGURE 41-12.1

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Skin graft harvest.

3. **Perineal Incision.** The patient then is placed in dorsal lithotomy position, perineal cleansing is performed, and a Foley catheter is placed.

   The lower edge of each labia minora is grasped with Allis clamps and extended laterally. A third Allis clamp is placed on the vestibular skin below the urethra and is lifted superiorly. A dimple in the vestibule typically is identified below the urethra. A 2- to 3-cm transverse incision is made sharply across it. Allis clamps then are placed on the inferior and superior edges of this incision and retracted.

4. **Neovaginal Dissection.** In creation of the new vagina, the goal is to create a canal that is bounded anteriorly by the fascia that supports the urethra and bladder. Posterior limits involve the perirectal fascia and rectum, and lateral borders are the pubococcygeus muscles. Each canal is created to reach a depth of approximately 12 cm, but entering the cul-de-sac of Douglas peritoneum should be avoided.

   Initially, two canals are created on either side of the median raphe. The raphe is a midline collection of dense connective tissue bands that stretch between the urethra and bladder above and the rectum below (Fig. 41-12.2). These canals are formed initially using a spreading motion with blunt-tipped scissors. Fingers then are insinuated into the forming canals. Pressure is exerted cephalad to extend the canal depth. Additionally, the finger pads are rolled outward, and lateral pressure is applied to widen the canal. Posterior pressure should be avoided to prevent entering the rectum.

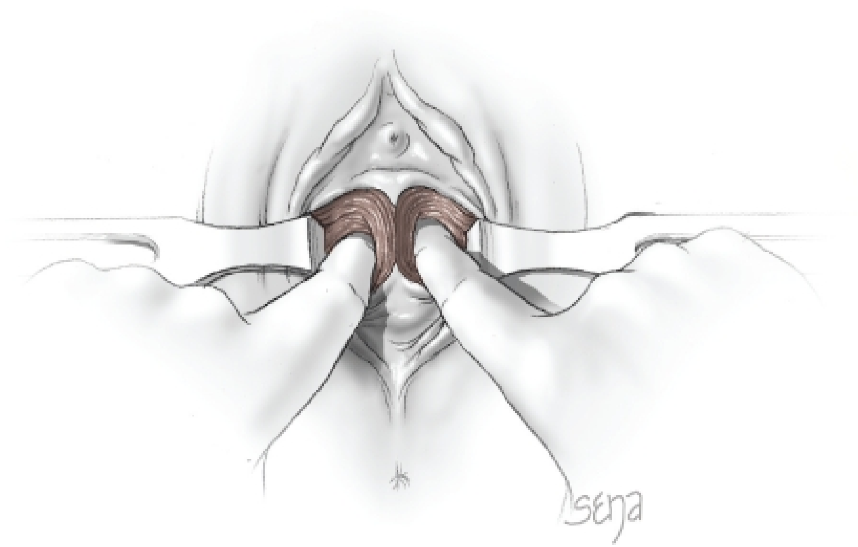
   During dissection, several points are noteworthy. First, with initial distal dissection, the surgeon may meet greater resistance than with the tissues more cephalad. Secondly, remaining in the correct dissection plane can be difficult. Accordingly, during dissection, a finger may be placed by the surgeon into the rectum to identify its location and avert perforation. Similarly, the Foley catheter may serve as an orientation tool anteriorly.

   To expand the space, retractors can be placed along the lateral walls of the forming canals and stretched outward. Moreover, incising the medial fibers of the pubococcygeus muscles can add width. These muscles are cut along the lateral aspect of each canal and at a level midway along the length of the canals.

   Cephalad, the canal is extended to within 2 cm of the cul-de-sac of Douglas. This leaves a beneficial layer of connective

tissue affixed to the peritoneum. First, the skin graft will attach more effectively to this connective tissue than to a smooth peritoneal surface. Second, rates of subsequent enterocoele formation are lowered.

FIGURE 41-12.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Neovaginal dissection.

5. **Cutting the Median Raphe.** On completion of the two smaller canals, the median raphe is cut. The final single canal measures approximately 10 to 12 cm deep and three fingerbreadths wide.

6. **Hemostasis.** Following surgery, collections of blood can separate the mold from the canal bed. Thus, hemostasis is required prior to mold insertion.

7. **Mold Preparation.** Attention then is directed to covering the vaginal mold with the harvested skin. The graft is removed from the saline bath. One end of the graft is placed at the base of the mold with the external surface of the skin facing the mold. The long axis of the graft is laid parallel to the long axis of the mold. The graft then is draped up and over the mold tip (Fig. 41-12.3).

   The lateral edges of the skin graft then are approximated on either side of the mold using interrupted suture of 3-0 catgut.

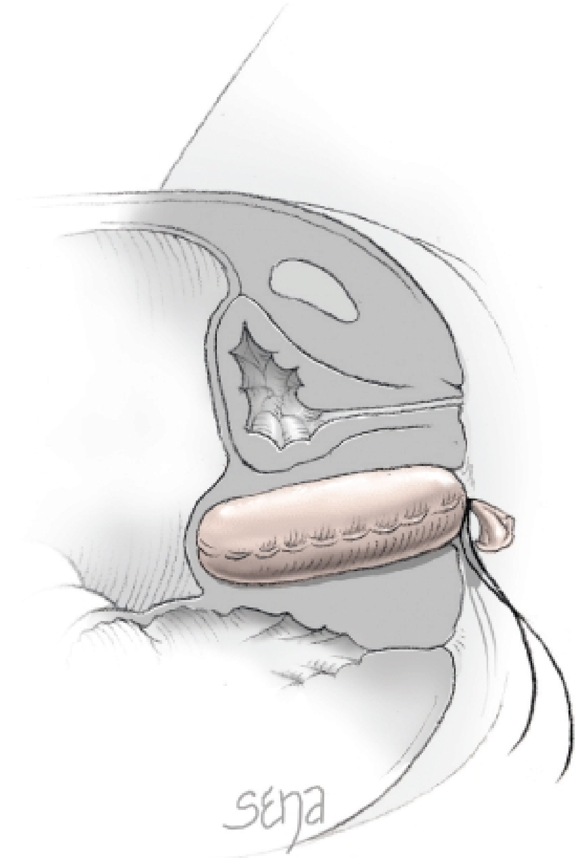
FIGURE 41-12.3

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Skin graft placed around soft mold.

8. **Mold Customizing.** Customizing the mold to the size of the created neovaginal canal is essential. If a mold width is too large, it can cause pressure necrosis or inhibit adequate drainage, which, as noted earlier, can lead to tissue maceration. Moreover, at the time of postoperative mold removal, a mold that is too large and snuggly fitted into the neovagina may pull the graft loose. Once the mold is sized and constructed appropriately, it is inserted (Fig. 41-12.4).

FIGURE 41-12.4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Skin graft and mold in place.

9. **Perineal Sutures.** The edges of the skin graft at the distal end of the mold then are re-approximated circumferentially to the distal opening of the neovagina using 4-0 or 5-0 delayed-absorbable suture.

   The labia minora, if sufficiently long, can be sutured together along the midline with 2-0 silk sutures to help hold the mold in place for the first 7 postoperative days. An elastic compression dressing is placed on the perineum.

Postoperative

The soft mold and Foley catheter are left in place for 7 days following surgery. To minimize dislodgement of the mold and wound contamination, a low-residue diet and loperamide 2 mg bid orally is used to limit defecation.

At the time of mold removal, an operating room, general anesthesia, and dorsal lithotomy position are employed. Stitches in the labia minora are cut, and the mold is removed. To lessen the risk of graft avulsion, irrigation is used to reduce adherence between graft and mold.

Several schedules for postoperative dilatation have been described. Commonly, the size of the mold placed at surgery is too large for maintenance use. Therefore, a smaller mold may be used initially and then gradually replaced with larger ones as the vagina stretches. For the first 6 weeks following surgery, the dilator is worn continuously except during defecation. During the subsequent 6 weeks, it is used only at night. Following these initial 3 months, patients then are instructed to either wear the dilator at night or engage in intercourse twice each week.

41-13 TREATMENT OF ECTOCERVICAL PREINVASIVE LESIONS

Cervical Cryotherapy

Cryotherapy has been used for decades to safely and effectively eliminate cervical intraepithelial lesions. This tool uses compressed gas to create extremely cold temperatures, which necrose cervical epithelium. In theory, as compressed gas expands, it draws heat away from its surroundings, in this case from the cervical epithelium.

An interfacing tip made of silver or copper, called the *cryoprobe,* allows contact and conduction of extreme cold across the surface of the cervix. When nitrous oxide gas is used, probe temperatures can reach â€“65Â°C, and cell death occurs at â€“20Â°C (Ferris, 1994; Gage, 1979).

As the cervical epithelium is cooled, an expanding layer of ice, called the *iceball,* forms beneath the center of the cryoprobe and grows circumferentially outward and past the margins of the probe. The portion of the iceball in which temperatures fall below â€“20Â°C is termed the *lethal zone.* This zone extends from the center of the cryoprobe to a point 2 mm inside the outer iceball edge. Outside this 2-mm point, tissue temperatures are warmer, and necrosis may be incomplete.

The expanding iceball grows in depth as well as circumference during treatment. Although this dimension cannot be seen, iceball depth is estimated to equal the lateral spread of the iceball away from the cryoprobe margin. To treat the endocervical glandular crypt involvement of most lesions, a depth of 5 mm is sufficient (Anderson, 1980; Boonstra, 1990a). For this reason, when cryotherapy is performed, the iceball is allowed to enlarge until reaching a mark 7 mm distal to the probe margin. This will ensure creation of a freezing depth of 7 mmâ€”a 5-mm lethal zone and a 2-mm zone of indeterminant tissue death (Ferris, 1994).

Many surgeons use a double-freeze method for cryotherapy in which time rather than iceball dimensions define the process. Refrigerant gas is delivered for 3 minutes to create the iceball. After this, the iceball is allowed to thaw for 5 minutes, at which point a second 3-minute freeze is performed (Creasman, 1984). Studies show that a single freezing period should be avoided because of associated high rates of dysplasia recurrence in the first year following treatment (Creasman, 1984; Schantz, 1984).

The specific indications and long-term rates of success for cryotherapy are discussed in Chapter 29, Cryosurgery. In general, cryotherapy is appropriate for squamous cervical intraepithelial lesions that do not extend deeper than 5 mm into the endocervical canal, do not span more than two quadrants of the ectocervix, and are not associated with unsatisfactory colposcopic examination or abnormal glandular cytology.

Preoperative

PATIENT EVALUATION

In the United States, women receive colposcopic evaluation and histologic interpretation of cervical biopsies prior to cryotherapy. Recently, a "see and treat" approach has been discussed in which immediate treatment rather than biopsy is initiated during colposcopy for abnormal cervical cytology (Dainty, 2005; Numnum, 2005). However, this type of approach, particularly in low-resource settings, is most successful when linked with excisional and not ablative procedures.

CONSENT

Although cryotherapy complications are uncommon, women should be counseled on expected postoperative changes and surgical risks. Watery vaginal discharge and vaginal spotting both may persist for several weeks following treatment. Fortunately, severe hemorrhage is rare (Denny, 2005). Abdominal cramping is common but typically subsides within the first 24 hours. Infrequently, women may experience a vasovagal reaction during treatment, and care should be supportive.

Surgical consents include both short- and long-term effects and typically describe risks for cervical stenosis, pelvic inflammatory disease (PID), and treatment failure. Rates for stenosis and PID are very low, and treatment failures for cervical intraepithelial neoplasia (CIN) I and II have been cited at 6 to 10 percent (Benedet, 1981, 1987; Jacob, 2005; Ostergard, 1980). In addition, Jobson and Homesley (1984) reported retraction of the squamocolumnar junction into the endocervical canal in patients following cryotherapy. In their study, postoperative surveillance revealed that this retraction resulted in a 47-percent rate of subsequent inadequate colposcopic examination, which often required more invasive evaluation. Infertility and pregnancy complications have not been associated with this treatment modality (Weed, 1978).

PATIENT PREPARATION

Ideally, cryotherapy is performed after completion of menstruation. This decreases the chances of pregnancy and allows cervical healing prior to the next menses. If it is performed prior to menses, postoperative swelling can block menstrual flow and intensify cramping. Before cryosurgery, a normal bimanual examination should be confirmed. If there is a possibility of pregnancy, β-hCG level testing should precede treatment.

Intraoperative

INSTRUMENTS

Cryotherapy typically requires a tank of refrigerant gas plus a cryogun, connecting tubing, pressure gauge, and cryoprobe. Nitrous oxide is the most commonly used refrigerant gas, although carbon dioxide also has been employed. A 20-lb tank is sufficiently large to deliver gas under the necessary 20 lb of pressure needed to cool tissues adequately. In contrast, smaller tanks may fail to generate sustained pressures and may hinder formation of a sufficiently large iceball. Gas moves through connecting tubing into the barrel of the cryogun and then to the cryoprobe tip. Circumferential grooves within the cryoprobe stem allow it to be attached securely into position at the end of the cryogun.

Selection of an appropriate probe is individualized but should cover the transformation zone and lesion. For this reason, cryoprobes come in different sizes and shapes (Fig. 41-13.1). For example, flat-faced probes are used for lesions located on the cervical portio. Advantageously, this shape has a lower tendency to push the resulting squamocolumnar junction toward the endocervical canal. This decreases the risk of unsatisfactory colposcopic examination following treatment (Stienstra, 1999). Use of smaller (19 mm) flat probes, however, has been discouraged following studies that indicated insufficient lethal zones and tissue destruction (Boonstra, 1990b; Ferris, 1994). Cone-shaped probes and those with nipple-shaped tips allow extension of the iceball into the endocervical canal. To minimize cervical stenosis, however, such nipple tips should not measure longer than 5 mm.

FIGURE 41-13.1

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Cryomachine and variety of cryoprobes tips. (Courtesy of CooperSurgical.)

Prior to treatment, the gas tank valve is opened, and the pressure gauge should indicate delivery of 20 lb of pressure. The cryogun trigger is squeezed to confirm that the cryoprobe cools adequately and that no excess gas escapes at the junction of cryogun and cryoprobe. Soft hissing is expected, but loud hissing and gas escape indicate that the loud rubber O-ring found between these two pieces should be replaced.

Surgical Steps

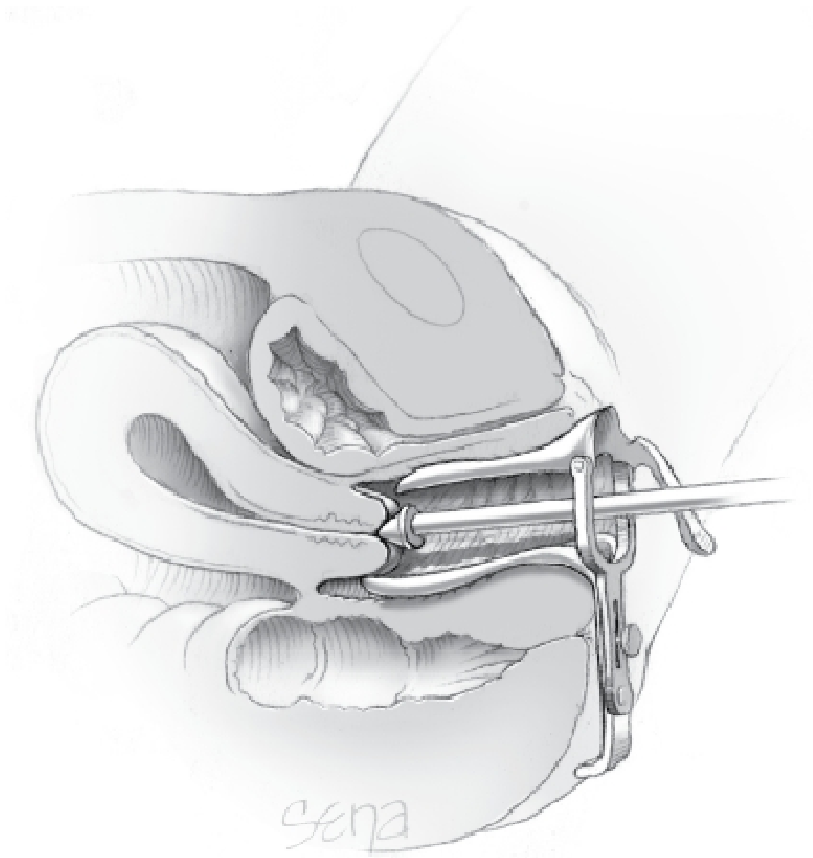
1. **Analgesia and Patient Positioning.** Cryotherapy may be performed in an office setting and requires no significant analgesia. However, to help attenuate associated uterine cramping, women commonly are given a nonsteroidal anti-inflammatory drug (NSAID) such as naproxyn sodium 550 mg orally 30 to 60 minutes prior to therapy. Although not used routinely, paracervical block and cervical subepithelial injection of 1-percent lidocaine have been associated with decreased pain scores (Harper, 1997, 1998).

   The patient is positioned in the dorsal lithotomy position, and a speculum is placed. No vaginal cleansing prep is required. The appropriate-sized cryoprobe is attached onto the end of the cryogun barrel. A water-based lubricant jelly is smeared on the end of the cryoprobe to ensure even tissue contact.

2. **Cryoprobe Placement.** The probe then is pressed firmly against the cervix (Fig. 41-13.2). The cryogun trigger is squeezed, a light hissing sound typically is heard, and frost begins to cover the probe.

   The cryoprobe should not contact the vaginal sidewalls. If this is identified, gas delivery is stopped to allow probe warming. The probe then is gently teased away from the wall, after which the procedure is continued.

FIGURE 41-13.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Cryoprobe placement.

3. **Iceball Formation.** The trigger is held until the iceball extends 7 mm distal to the outer margin of the cryoprobe (Fig 41-13.3). Freezing typically requires 3 minutes. During the freezing process, ice may form that blocks the gas tubing. For this reason, many manufacturers recommend pushing the defrost button for less than 1 second every 20 seconds during freezing.

FIGURE 41-13.3

A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photographs of cryotherapy. **A.** Cryotip applied to cervix. **B.** Creation of advancing iceball. (Courtesy of Dr. Claudia Werner.)

4. **First Thaw.** At this point, the trigger is released. The probe quickly warms and can be removed from the cervix. Attempts to remove the probe prior to its complete defrosting can cause patient discomfort and bleeding. The surface of the cervix is allowed to thaw during the following 5 minutes.

5. **Second Cycle.** Subsequently, the freezing cycle is repeated for an additional 3 minutes. At completion of the second cycle, the cryoprobe and then the speculum are removed. Because vasovagal responses can be seen with this procedure, patients are assisted to a sitting position slowly.

Postoperative

Copious watery vaginal discharge that develops after treatment usually requires sanitary pad use, and tampons are discouraged. Although some advocate dÃ©bridement of the necrotic eschar to decrease the amount of discharge, Harper and colleagues (2000) reported no affect in the amount or duration of this discharge with such dÃ©bridement. Vaginal spotting is expected and can persist for weeks, but hemorrhage is rare. During the first few days following cryotherapy, patients may complain of diffuse mild lower abdominal pain or cramping, for which NSAIDs typically provide relief. Infrequently, severe pain and cramping may result from necrotic tissue obstructing the endocervical canal and is termed *necrotic plug syndrome.* Removal of the obstructing tissue typically resolves symptoms.

Because a large area of the cervix is denuded after cryotherapy, there is an increased potential for infection. Accordingly, patients should abstain from intercourse during the 4 weeks following surgery. If abstinence is not feasible, then condom use is encouraged.

Depending on patient symptoms, work and exercise may resume following treatment.

Loop Electrosurgical Excision Procedure

Loop electrosurgical excision procedure (LEEP), also known as *large loop excision of the transformation zone* (LLETZ), uses electric current to generate energy waveforms through a metal electrode that either cuts or desiccates cervical tissues. These thin wire semicircular electrodes allow clinicians to excise cervical lesions in an office setting with minimal patient discomfort, cost, and complications. In addition, LEEP permits submission of a surgical specimen for additional evaluation. In the United States, electrosurgical treatment of CIN is popular and often preferred over cryotherapy or laser ablation (see Chap. 29, Loop Electrosurgical Excision Procedure).

Preoperative

PATIENT EVALUATION

As with cryotherapy and laser ablation, women in the United States undergo colposcopy and histologic review of colposcopic biopsies prior to LEEP. Preoperative patient preparation mirrors that for cryotherapy (Patient Preparation).

CONSENT

This procedure is associated with low morbidity, and overall complication rates approximate 10 percent (Dunn, 2004). Major complications are rare (0.5 percent) and may include bowel or bladder injury and hemorrhage (Dunn, 2003; Kurata, 2003). Short-term complications such as abdominal pain, vaginal bleeding, vaginal discharge, and bladder spasm may be treated symptomatically.

Long-term complications include failure to treat the cervical lesion completely and cervical stenosis. Persistent disease typically is noted in initial surveillance PAP smear testing following LEEP (see Chap. 29, Further Cytologic and Colposcopic Surveillance). However, such treatment failure rates are low (approximately 5 percent) and are positively correlated with initial excised lesion size (Alvarez, 1994; Gunasekera, 1990; Mitchell, 1998). Cervical stenosis is estimated to complicate less than 6 percent of cases, and risk factors include the presence of an endocervical lesion and excision of a large tissue volume (Baldauf, 1996; Suh-Burgmann, 2000).

The effects of LEEP and obstetric outcomes are unclear. Several studies have shown that pregnancy does not appear to be adversely affected by LEEP, whereas meta-analysis reviews by others have noted increased risks of premature labor and premature rupture of the membranes (Crane, 2003; Cruickshank, 1995; Ferenczy, 1995; Kyrgiou, 2006; Tan, 2004a).

Intraoperative

INSTRUMENTS

Tissue excision during LEEP requires an electrosurgical unit, wire loop electrodes, insulated speculum, and smoke evacuation system. Electrosurgical units used in LEEP procedures generate high-frequency (350 to 1200 kHz), low-voltage (200 to 500 V) electric current. Because of the risk for electrical burns to the patient from stray current, grounding pads should contact patients on conductive tissue that is close to the operative site (see Chap. 40, Patient Grounding).

Similarly, an insulated speculum is used in LEEP procedures to limit the risk of stray current conductance to the patient. The insulated speculum should have a port for smoke evacuation tubing, which assists in clearing smoke from the operating field to improve visualization.

Surgical smoke plumes have contents including carbon monoxide, polyaromatic hydrocarbons, and a variety of trace toxic gases (National Institute for Occupational Safety and Health, 1999). Although there has been no documented transmission of infectious disease through surgical smoke, the potential for generating infectious viral fragments may exist. For these reasons, local smoke evacuation systems are recommended.

Electric current is directed to tissue via a 0.2-mm stainless steel or tungsten wire electrode that comes in a variety of sizes customized to treat lesions of various sizes (Fig. 41-13.4). These instruments are disposable and are discarded after each patient procedure.

FIGURE 41-13.4

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Variety of loop electrosurgical excision procedure (LEEP) electrodes. (Courtesy of Utah Medical Products, Inc.)

Surgical Steps

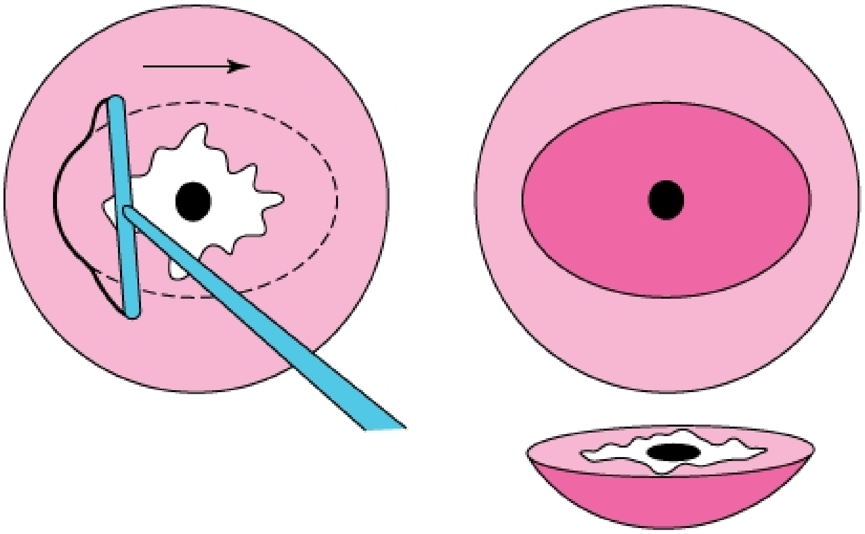
1. **Anesthesia and Patient Positioning.** The patient is placed in the dorsal lithotomy position, and the electrosurgical grounding pad is placed on the upper thigh or buttock. The insulated speculum is inserted into the vagina, and smoke evacuation tubing is attached. The application of Lugol solution outlines lesion margins before starting the procedure (see Chap. 29, Lugol Solution). For most patients, LEEP is an office procedure, typically performed under local analgesia. Vasoconstricting solutions of either pitressin and 1-percent lidocaine solution (10 units pitressin in 30 mL of lidocaine) or 1-percent lidocaine and epinephrine (1:100,000 dilution) may be used. A 25- to 27-gauge needle is used to circumferentially inject 5 to 10 mL of either solution 1 to 2 cm deep into the cervix outside the area to be excised. Cervical blanching should be seen.

2. **Single-Pass Excision.** Ideally, the lesion should be excised in one pass, and the appropriately sized loop is selected for this goal. If colposcopy is satisfactory, the correct loop diameter should incorporate the entire lesion diameter to a depth of 5 to 8 mm. The electrosurgical unit is set to cutting mode, and typically 30 to 50 W is used depending on loop size. Larger loops require higher wattage.

   To excise the lesion, a loop is positioned 3 to 5 mm outside the lateral perimeter of the lesion (Fig. 41-13.5). Current through the loop is activated prior to tissue contact, during which electric sparks at the loop tip may be seen. The loop is introduced to the cervix at a right angle to its surface. The loop is drawn parallel to the surface until a point 3 to 5 mm outside the opposite border of the lesion is reached. The loop then is withdrawn slowly, positioning it at right angles to the surface. Current is stopped as soon as the loop exits the tissue.

Following excision, the specimen is placed in formalin for pathologic evaluation.

FIGURE 41-13.5

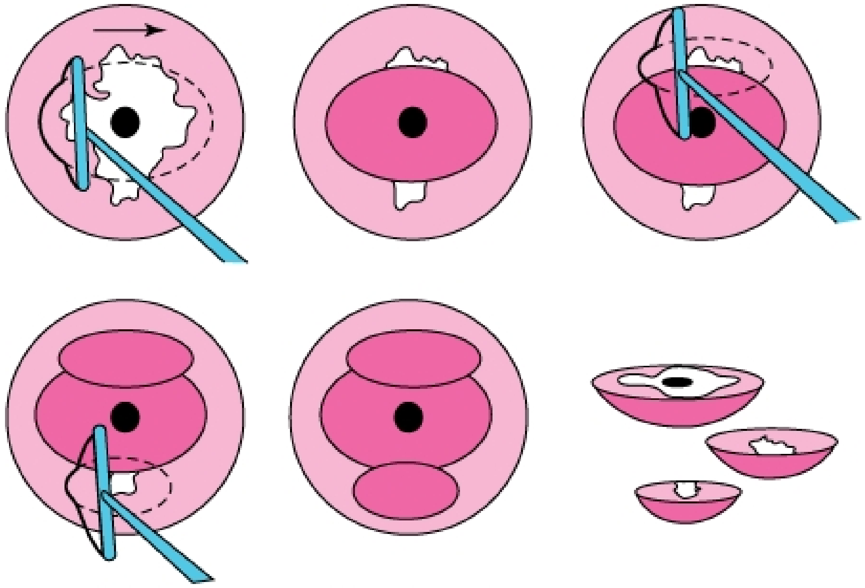


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Single-pass excision procedure.

3. **Multiple-Pass Excision.** Less commonly, bulky lesions may require multiple passes using a combination of loop electrode sizes (Fig. 41-13.6).

FIGURE 41-13.6



Multiple-pass excision procedure.

4. **Control of Bleeding Sites.** Despite use of vasoconstrictors, bleeding following LEEP is common. Sites of active bleeding may be controlled using a 3- or 5-mm ball electrode and the electrosurgical unit switched to coagulation mode. Alternatively, Monsel solution can be applied with direct pressure to bleeding sites.

Postoperative

Following excision, patients typically will experience light spotting and cramping. Postoperative healing and patient care in general follow those for cryotherapy (Postoperative).

Carbon Dioxide Cervical Laser Ablation

The carbon dioxide (CO_2) laser produces a beam of infrared light with a wavelength of 10.6 μm. At its focal point, the laser energy produces heat sufficient to boil intracellular water and vaporize tissue.

Indications and success rates are discussed more fully in Chapter 29, Carbon Dioxide Laser. In general, laser ablation may be used in patients in whom the entire transformation zone can be seen during satisfactory colposcopy. There should be no evidence of microinvasive, invasive, or glandular disease, and cytology and histology should correlate positively (Martin-Hirsch, 2000).

Although research has shown laser ablation to be an effective tool in treating CIN, its popularity is decreasing. Laser units are significantly more expensive than those used for cryotherapy and LEEP. In addition, lesions are destroyed with ablation, and unlike LEEP, the opportunity for additional pathologic evaluation of surgical margins is lost. Finally, physician and staff training and certification typically are required for safe, effective use of laser equipment.

Preoperative

CONSENT

Laser ablation is considered a safe and effective means to treat CIN. As with any treatment of cervical dysplasia, patients should be counseled on the risks of disease persistence and recurrence following treatment. These risks and surgical complications are low and comparable with those of LEEP (Alvarez, 1994; Nuovo, 2000).

Intraoperative

INSTRUMENTS

Carbon dioxide laser machines suitable for cervical ablation are mobile, self-contained units. Tissue effects vary depending on the interval at which energy bursts are released. As a result, continuous waves (cutting) or pulsed energy (coagulation) can be released.

Because laser light is reflective, protective eye wear is required for all participants, and a sign is posted on the suite door warning that a laser procedure is in progress. For this same reason, a matte-surface speculum is necessary. As with LEEP, noxious smoke is generated, and a smoke evacuation system is recommended.

Surgical Steps

1. **Anesthesia and Patient Positioning.** Laser ablation for many women is an outpatient procedure performed in either an operating suite or an office depending on laser equipment location. In most cases, local analgesia combined with a vasoconstrictor is sufficient, and administration mirrors that used for LEEP (Surgical Steps). The patient is placed in the dorsal lithotomy position. A matte-surfaced speculum is inserted, and smoke evacuation tubing is attached to a port on the speculum. Misdirected laser energy can burn surrounding tissues and ignite paper drapes. Therefore, moistened cloth towels are draped outside the vulva to absorb errant energy. To delineate the area of excision, Lugol solution is applied.

2. **Laser Settings.** The colposcope-laser assembly is brought into position and focused on the ectocervix. The laser is set to achieve a power density (PD) of 600 to 1200 W/cm^2 in a continuous-wave mode.

3. **Ablation.** Initially, four dots are ablated at 12, 3, 6, and 9 o'clock positions on the perimeter of the ectocervix to surround the entire lesion. These dots serve as landmarks and are connected in an arching pattern to create a circle. Once encircled, the area is ablated to a depth of 5 to 7 mm (Fig. 41-13.7).

FIGURE 41-13.7

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Cervical bed following laser ablation. (Courtesy of Dr. Eddie McCord.)

4. **Endocervical Eversion.** To help prevent postoperative retraction of the squamocolumnar junction cephalad into the endocervical canal, the tissue immediately surrounding the endocervix is ablated less deeply. This allows the endocervical lining to evert.

5. **Hemostasis.** During ablation, bleeding is common. A defocused laser beam and a lower power setting in a super-pulse-wave mode will coagulate vessels and aid hemostasis. At the end of surgery, bleeding also may be controlled with an application of Monsel solution.

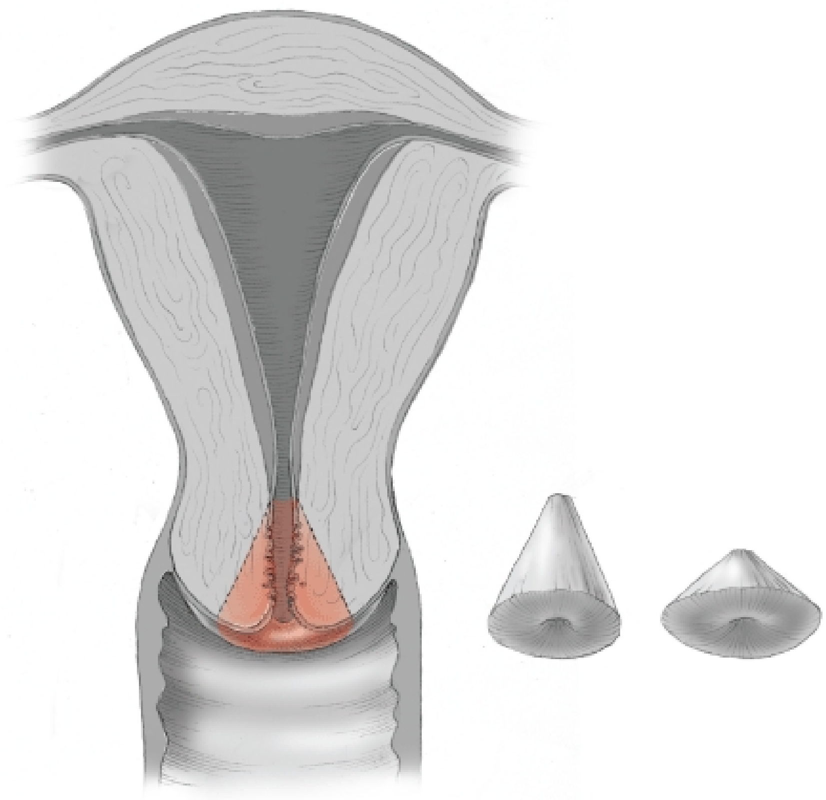
Postoperative

Cramping is common following surgery, and light bleeding may persist for a week. Postoperative patient counseling is similar to that for LEEP.

41-14 CERVICAL CONIZATION

Cervical conization removes ectocervical lesions and a portion of the endocervical canal by means of a cone-shaped tissue biopsy (Fig. 41-14.1). It is a safe, effective means to treat cervical intraepithelial neoplasia (CIN), carcinoma in situ (CIS), and adenocarcinoma in situ (AIS). Moreover, cervical conization is the standard treatment for women with unsatisfactory colposcopy, positive endocervical curettage, and discordant cytology and histology. Excision may be completed via scalpel, termed *cold-knife conization.* Alternatively, laser or loop electrosurgical excision procedure (LEEP) conization may be performed. Success rates for these excisional methods in the treatment of CIN have been found equivalent. However, LEEP conization has gained in popularity because of its ease of use and cost-effectiveness (Martin-Hirsch, 2000; Mitchell, 1998). Indications for and differences among these modalities are discussed in Chapter 29, Excisional Treatment Modalities.

FIGURE 41-14.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Cone-shaped tissue biopsies.

Preoperative

PATIENT EVALUATION

Prior to conization, women will have undergone colposcopic examination and histologic evaluation of biopsies. Beta human chorionic gonadotropin (β-hCG) testing is warranted prior to conization if pregnancy is suspected. If pregnancy is confirmed and invasion is not suspected colposcopically, postpartum management is reasonable. Conization during pregnancy has great morbidity because of increased vascularity and bleeding.

CONSENT

Risks associated with conization mirror those for LEEP excision of ectocervical lesions. However, cold-knife conization has a greater risk of bleeding compared with laser and LEEP conization. Moreover, cold-knife and laser conizations carry higher risks of cervical stenosis compared with LEEP conization (Baldauf, 1996; Houlard, 2002). Increasing patient age and depth of endocervical excision are significant cervical stenosis risks. Penna and co-workers (2005) noted a lower risk of stenosis in postmenopausal women using estrogen-replacement therapy compared with postmenopausal nonusers.

Conization of the cervix for the treatment of CIN has been associated with adverse outcomes in subsequent pregnancies, including preterm delivery, low-birth-weight infants, incompetent cervix, and cervical stenosis (Crane, 2003; Kristensen, 1993a, 1993b; Raio, 1997; Samson, 2005). Although there is no major difference in obstetric outcome among the three techniques, increased cone biopsy size has been shown to correlate positively with rates of preterm delivery and premature membrane rupture (Mathevet, 2003; Sadler, 2004). Cold-knife conization generally removes more cervical stroma than other excisional methods.

Cold-Knife Conization

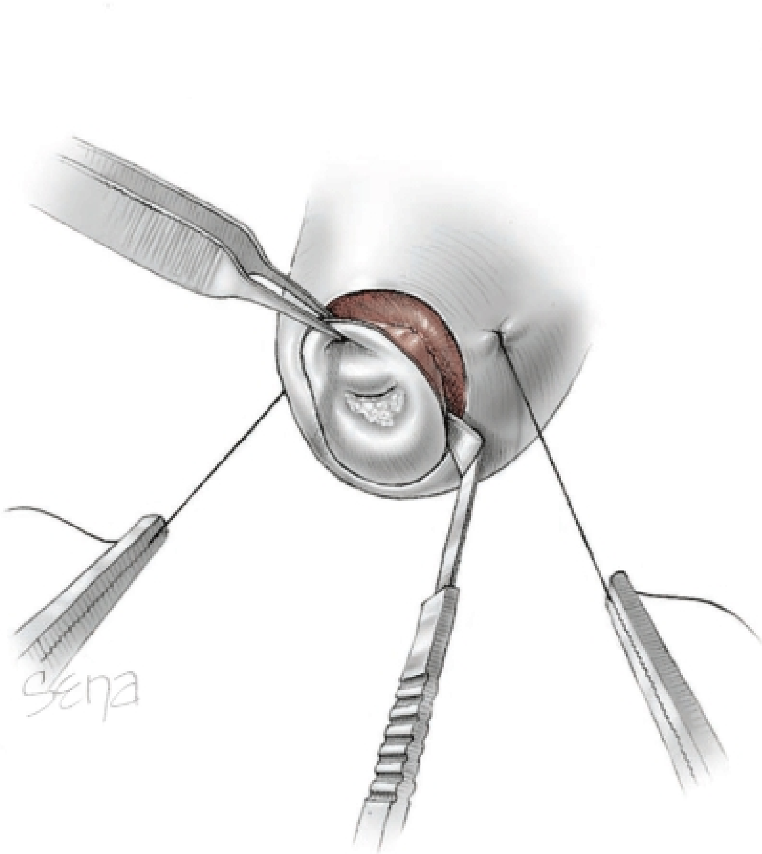
Surgical Steps

1. **Anesthesia and Patient Positioning.** For most women, cold-knife conization is a day-surgery procedure performed under general or regional anesthesia. Following administration of anesthesia, the patient is placed in the dorsal lithotomy position. The vagina is surgically prepared, the bladder is drained, and vaginal sidewalls are retracted to reveal the cervix. Areas of planned excision may be identified more easily following Lugol solution application (see Chap. 29, Lugol Solution).

2. **Injection of Vasoconstrictors.** Bleeding during cold-knife conization can be brisk and obscure the operating field. Accordingly, preventative steps can be taken both before and during surgery. First, vasoconstrictors as described for LEEP are injected circumferentially into the cervix. Additionally, descending cervical branches of the uterine arteries can be ligated with figure-of-eight sutures using a nonpermanent material placed along the lateral aspects of the cervix at 3 and 9 o'clock. After these knots are secured, the sutures are kept long and held by hemostats to manipulate the cervix.

3. **Conization.** A uterine sound or small-caliber uterine dilator is placed into the endocervical canal to orient the surgeon as to the depth and direction of the canal. Using a Beaver blade or a no. 11 blade, the surgeon initiates the incision on the lower lip of the cervix. This limits blood from obscuring the operative field. A Beaver blade is a triangular-shaped knife blade with a 45-degree bend and is useful for creating incisions at an angle. A circumscribing incision creates a 2- to 3-mm border around the entire lesion (Fig. 41-14.2). The 45-degree angle of the blade is directed centrally and cephalad to excise a conical specimen. Toothed forceps or tissue hooks may be used to retract the ectocervix during creation of the cone. Scalpel or Mayo scissors may be used to cut the tip of the cone and release the specimen. Following excision, an orienting suture is placed on the site of the specimen that corresponds to the 12 o'clock position in situ. This orientation is noted on a pathology requisition form.

FIGURE 41-14.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Conization incision.

4. **Endocervical Curettage.** Following removal of the cone specimen, endocervical curettage is performed to screen for residual disease distal to the excised cone apex (Husseinzadeh, 1989; Kobak, 1995).

5. **Hemostasis.** Following excision of the specimen, bleeding is common and can be controlled with individual suturing of isolated vessels, with electrosurgical coagulation, or with Sturmdorf sutures. In addition, a topical absorbable hemostat mesh (Surgicel Nu-knit, Johnson and Johnson, Piscataway, NJ) can be placed in the cone bed.

   Sturmdorf suturing is a running locked suture line that closes the cone bed by circumferentially folding the cut ectocervical edge inward toward the endocervix. This technique is less favored because of increased rates of postoperative dysmenorrhea, inadequate postoperative surveillance PAP smears, and concerns that the flap might conceal residual disease (Kristensen, 1990; Trimbos, 1983).

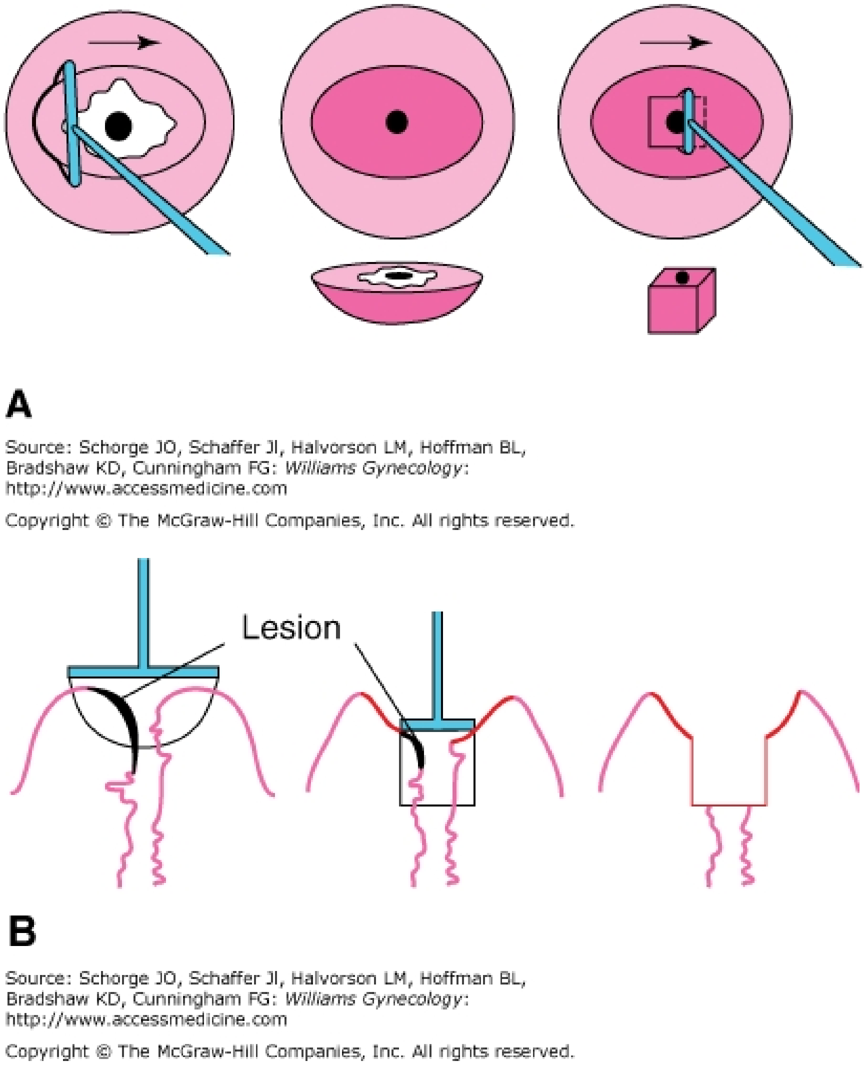
Loop Electrosurgical Excision Procedure Conization

Surgical Steps

The surgical steps for this more extensive LEEP mirror those used for excision of ectocervical lesions (Surgical Steps). However, to remove the endocervical canal, a deeper pass must be made through the cervical stroma. This may be accomplished with a single pass using a larger loop. Alternatively, in an effort to minimize the volume of tissue excised, a *tiered technique,* also known as *top-hat technique,* can be used. With this method, an initial pass is made to remove ectocervical lesions, as described previously (Fig. 41-13.5). To remove the endocervical canal, a second smaller loop is passed more deeply into the cervical stroma (Fig. 41-14.3).

As a result, the tissue is excised in two pieces and both are sent for evaluation.

FIGURE 41-14.3



Loop electrosurgical excision procedure (LEEP) "top hat" cervical conization procedure. **A.** View of procedure as seen through a speculum. Final specimen as two pieces. **B.** View is 90 degrees from that shown in A. The first pass is made with a round loop electrode. The deeper second pass is completed with a square loop electrode. Final shape of cervical conization bed.

Laser Conization

Excision of a laser cone-biopsy specimen uses similar techniques as those described for laser ablation (Surgical Steps). However, rather than ablating the involved tissue, laser energy is directed to cut and remove a cone-biopsy specimen. A higher wattage of 800 to 1200 W/cm^2 combined with a smaller laser spot size is used to create a cutting effect. A cone-shaped specimen then is excised. During excision of the cone specimen, nonreflective tissue hooks may be needed to retract the ectocervical edge away from the laser beam path and to create tissue tension along the plane of incision.

Postoperative

Recovery following all excisional methods is rapid and follows that for other surgeries of the cervix described previously (Postoperative). Patients require postoperative surveillance for identification of disease persistence or recurrence, and this is described in detail in Chapter 29, Further Cytologic and Colposcopic Surveillance.

41-15 WIDE LOCAL EXCISION OF VULVAR INTRAEPITHELIAL NEOPLASIA

With vulvar intraepithelial neoplasia (VIN), treatment goals include prevention of invasive vulvar cancer and, when possible, preservation of normal vulvar anatomy and function. Accordingly, although simple vulvectomy may be appropriate treatment in some cases, less extensive wide local excision of lesions and medical treatments described in Chapter 29, Management also have been evaluated as alternative options (Hillemanns, 2006).

Wide local excision of lesions is favored by many because it offers a tissue specimen for exclusion of invasive disease and confirmation of surgical margins and lowers patient morbidity. In patients in whom excision involves the clitoris, urethra, or anus, a combined surgical excision and laser ablation approach is sometimes helpful. This combined technique uses carbon dioxide (CO_2) laser therapy at sites where excision alone might lead to dysfunction or malformation (Cardosi, 2001).

Preoperative

PATIENT EVALUATION

Prior to excision, full evaluation of the lower reproductive tract for evidence of invasive disease should be completed as outlined in Chapter 29, Colposcopy.

CONSENT

Wide local excision of VIN successfully treats disease, and progression to invasive vulvar cancer is low (3 to 5 percent) (Jones, 2005; Rodolakis, 2003). However, VIN recurrence is common, and even in those with tissue margins negative for disease, recurrence ranges from 15 to 40 percent (Kuppers, 1997; Modesitt, 1998).

In the immunocompetent, surgical and postoperative risks are few and typically include wound infection or separation, chronic vulvodynia, dyspareunia, and scarring or altered vulvar appearance. Any vulvar operation requires thorough preoperative counseling regarding expectations for anatomic outcome and for sexual function.

Intraoperative

Surgical Steps

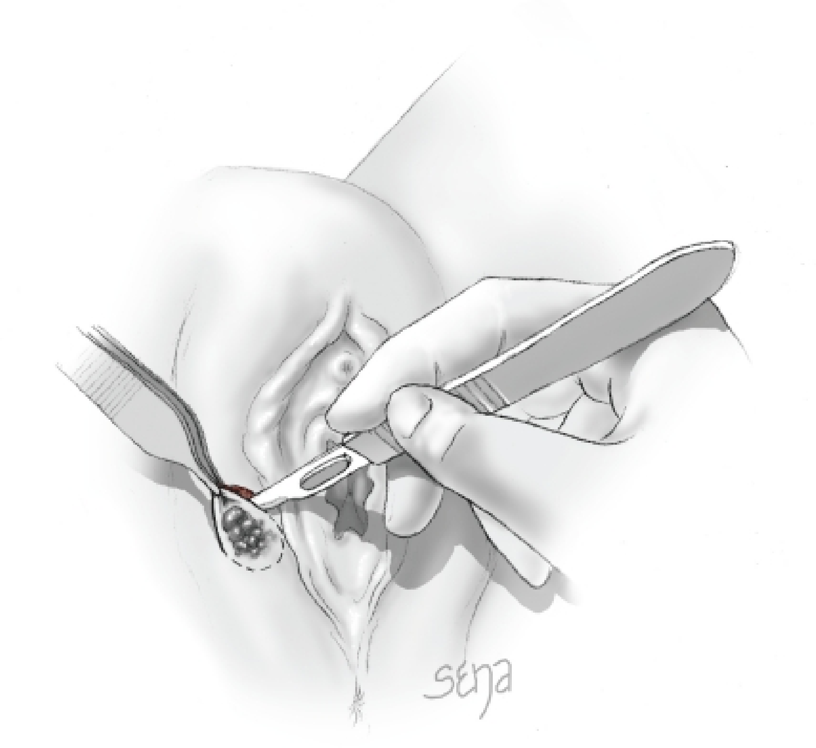
1. **Anesthesia and Patient Positioning.** The choice of anesthesia or analgesia will vary depending on the location and size of the lesion being treated. Whereas smaller and labial or perineal lesions may be excised easily using local analgesia in an office setting, larger lesions or those involving the urethra and clitoris may require general or regional anesthesia. The patient is placed in dorsal lithotomy position, and the vulva is surgically prepared.

2. **Lesion Identification.** Prior to incision, the area of excision should be well demarcated. Colposcopic examination following application of 3- to 5-percent acetic acid to the vulva will aid in identification of lesion margins. A 5-mm circumferential surgical margin surrounding the lesion is recommended by most (Joura, 2002). In the past, toluidine blue was used to stain nuclear chromatin and enhance vulvar lesions. However, normal tissue also can absorb the stain and distort true disease margins. Therefore, use of this stain is not recommended.

3. **Incision.** A scalpel in used to incise the lesion. Most VIN lesions fail to extend deeper than 2 mm on non-hair-bearing areas such as the labia minora. However, in hair-bearing areas of the vulva, VIN may extend to the deepest hair follicles (Fig. 41-15.1). This is generally deeper than 2 mm but not more than 4 mm. Thus, incision depth will vary depending on lesion location (Preti, 2005).

   Because disease recurrence is related to the presence or absence of disease-free surgical margins, frozen sections of the specimen margins can be evaluated intraoperatively (Friedrich, 1983).

FIGURE 41-15.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Vulvar incision.

4. **Margin Undermining.** To mobilize the wound edges for re-approximation, a surgeon undermines these edge margins sharply with fine scissors. Tissues should allow wound edge approximation without undue tension at the suture line.

5. **Wound Closure.** The edges of the skin then are reapproximated with interrupted stitches using 3-0 or 4-0 delayed-absorbable sutures.

Postoperative

Typically, without complication, recovery from wide local excision is rapid, and patients may resume normal activities as desired. Sitz baths and oral analgesics usually are recommended for the first week following surgery. Intercourse is delayed until wounds have fully healed, and this time will vary depending on wound site and size.

Because of the significant risk for VIN recurrence, postprocedural surveillance is essential, with colposcopic vulvar examination every 6 months for 2 years and then annually thereafter.

41-16 SHARP DILATATION AND CURETTAGE

Although used for diagnostic evaluation and treatment of abnormal uterine bleeding during the last 150 years, the indications for sharp dilatation and curettage (D&C) have decreased with the development of less invasive methods (see Chap. 8, Endometrial Biopsy). In the evaluation of abnormal uterine bleeding, sharp curettage may be used alone or more commonly in combination with

hysteroscopy for women with persistent bleeding despite normal findings with sonography and pipelle endometrial sampling. Moreover, when a stenotic cervical os prohibits in-office endometrial sampling, sharp D&C may be necessary to gain access to the uterine cavity. Additionally, in the treatment of severe acute menorrhagia, sharp D&C may be used to remove hypertrophic endometrium if bleeding is refractory to oral or intravenous estrogen administration. Although suction curettage is used more commonly for removal of products of first-trimester pregnancy, sharp D&C also may be an option. Finally, in case of suspected ectopic pregnancy, sharp D&C is sometimes used to document the absence of intrauterine trophoblastic tissue (see Chap. 7, Endometrial Sampling).

Preoperative

CONSENT

For most women, sharp D&C poses only a small risk of complication, and rates typically fall below 1 percent (Radman, 1963; Tabata, 2001). Among these, infection and uterine perforation are among the most common.

PATIENT PREPARATION

Because the indications for sharp D&C are diverse, diagnostic testing prior to evacuation will vary. Antibiotic administration prior to sharp D&C typically is not required. However, because pelvic infection may follow this procedure, antibiotics usually are prescribed postoperatively. Doxycycline 100 mg orally twice daily for 10 days is given commonly. The risk of bowel injury with this procedure is slight, and thus preoperative enemas are not mandatory.

Intraoperative

Surgical Steps

1. **Anesthesia and Patient Positioning.** Sharp D&C typically is performed as an outpatient procedure under general or regional anesthesia or with local nerve blockade combined with intravenous sedation. The patient is placed in the dorsal lithotomy position, the vagina is surgically prepared, and the bladder is drained.

   A bimanual examination to determine uterine size and inclination is performed prior to introduction of vaginal instruments. This step allows instruments to be inserted along the long axis of the uterus to avoid perforation.

2. **Uterine Sounding.** Suitable vaginal exposure can be achieved with either a Graves speculum or individual vaginal retractors. The anterior lip of the cervix is grasped with a single-tooth tenaculum to stabilize the uterus during sharp D&C (Fig. 40-21). A Simpson uterine sound then is held as a pencil with the thumb and first two fingers (Fig. 41-16.1). The sound is guided slowly through the cervical os, into the uterine cavity, and up to the fundus. Importantly, instruments should not be forced because this increases the risk of perforation.

   Once gentle resistance is met at the fundus, the distance from the fundus to the external os is measured by score marks along the length of the sound. Knowledge of the depth to which dilators and curettes can be inserted safely decreases the risk of uterine perforation.

   At times, cervical stenosis may preclude easy access to the endocervical canal. In these cases, smaller-caliber tools, such as a lacrimal duct probe, may be guided into the external cervical os to define the canal path. Sonography may be helpful when done simultaneously with sharp D&C in these situations. Visualization of instruments by sonography as they are being passed may help to ensure proper placement. In addition, for stenosis, pretreatment with the prostaglandin E1 analog misoprostol (Cytotec, Pharmacia, Morpeth, UK), 100 mg orally the night before and morning of biopsy may allow adequate cervical softening for instrument passage.

FIGURE 41-16.1

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Sims uterine sound.

3. **Uterine Dilatation.** Following sounding, dilators of sequentially increasing caliber are inserted to open the endocervical canal and internal cervical os. A Hegar, Hank, or Pratt dilator (see Fig. 41-17.4) is held by the thumb and first two fingers while the fourth and fifth fingers and heel of the hand rest on the perineum and buttock (Fig. 41-17.5). Each dilator is advanced gently and gradually through the internal cervical os. Serial dilatation continues until the cervix will admit the selected curette (Fig. 41-16.2).

   During sounding or dilatation, uterine perforation may occur and is suspected when the instrument travels deeper than previously measured. Because of the blunt, narrow shape of these tools, risk of significant uterine or abdominal organ injury is low. In such cases, if significant bleeding is absent, re-assessment of uterine inclination and completion of the sharp D&C are reasonable. Alternatively, surgery may be terminated and repeated at a later date, thus allowing myometrial healing.

FIGURE 41-16.2

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

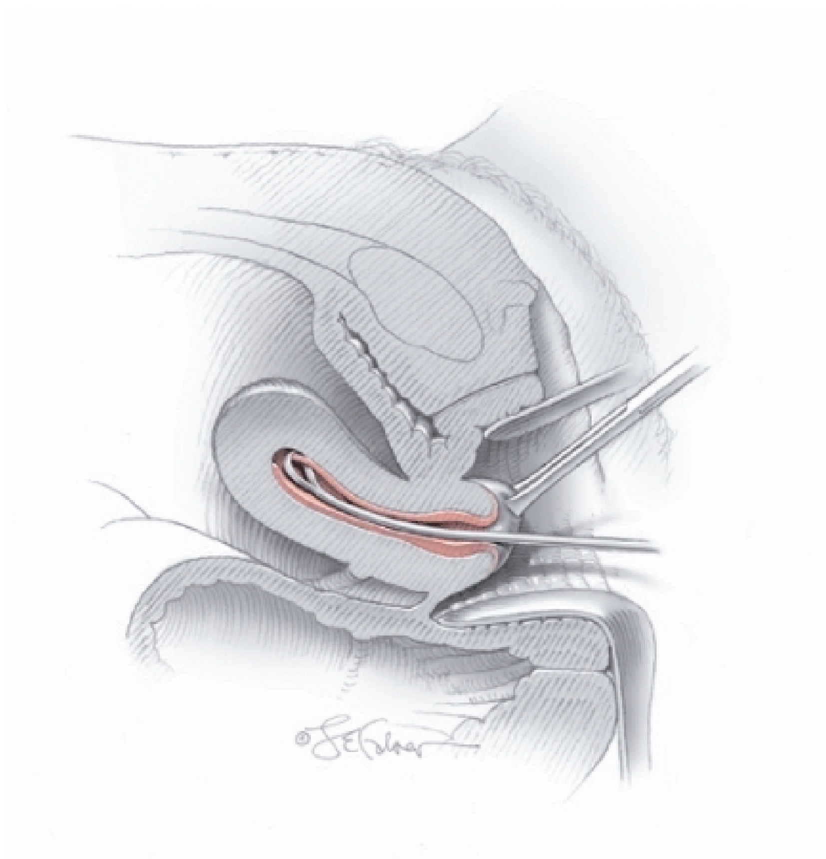
Uterine curette.

4. **Uterine Curettage.** Prior to curettage, a sheet of nonadherent wound dressing material (Telfa, The Kendall Company, Mansfield, MA) is spread out in the vagina beneath the cervix. The uterine curette then is inserted and advanced to the fundus, following the long axis of the corpus. On reaching the fundus, the sharp surface of the curette is positioned to contact the adjacent endometrium (Fig. 41-16.3). Pressure is exerted against the endometrium as the curette is pulled toward the internal cervical os.

   After reaching the os, the curette is redirected to the fundus and positioned immediately adjacent to the path of the first curettage pass. In this manner, the surgeon attempts to sample the entire uterine surface. After several serial passes, tissues collected in the isthmus region are scraped out onto the Telfa pad.

   As with dilatation, the uterus may be perforated during curettage. However, the sharp curette has the potential to lacerate bowel, vessels, and other abdominal organs. Accordingly, diagnostic laparoscopy is suggested to evaluate for such injuries.

FIGURE 41-16.3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Uterine curettage.

5. **Uterine Exploration.** Because uterine polyps, both large and small, may be missed with sharp curettage, uterine exploration with Randall kidney stone forceps is warranted in women undergoing evaluation of abnormal bleeding. Closed forceps are inserted into the endometrial cavity. On reaching the fundus, the forceps are opened against the uterine walls, closed, and then pulled away from the endometrium. In this fashion, anterior, posterior, proximal, and distal cavity surfaces are explored. With capture of a polyp within the jaws, a tug against the closed forceps is felt as they are pulled away from the uterine wall. Firm traction typically frees the polyp.

   Alternatively, hysteroscopy may be used adjunctively with curettage to diagnose and remove focal lesions such as polyps.

Postoperative

Recovery from sharp D&C is typically fast and without complication. Light bleeding or spotting is expected, and patients may resume normal activities at their individual paces.

41-17 SUCTION DILATATION AND CURETTAGE

Suction dilatation and curettage (D&C) is the most common method used to remove first-trimester products of conception (see Chap. 6, Surgical Abortion). Vacuum aspiration, the most common form of suction curettage, requires a rigid cannula attached to an electric-powered vacuum source. Alternatively, manual vacuum aspiration uses a similar cannula that attaches to a hand-held

syringe for its vacuum source (MacIsaac, 2000; Masch, 2005).

Preoperative

PATIENT EVALUATION

For most women, suction D&C is preceded by transvaginal sonography. As discussed in Chapter 6, Threatened Abortion, this imaging modality aids in documenting pregnancy viability, location, and size. In addition to sonographic evaluation, blood typing is performed to assess Rh status. Administration of 50 or 300 µg (1,500 IU) Rho [D] immune globulin intramuscularly within 72 hours of pregnancy termination in Rh-negative women can lower the risk of isoimmunization in future pregnancies dramatically.

CONSENT

Suction D&C is a safe and effective method of uterine evacuation (Forna, 2001). Short-term complication rates are low and have been cited at 1 to 5 percent (Hakin-Elahi, 1990; Zhou, 2002). Complications include uterine perforation, retained products, infection, and hemorrhage, and rates increase after the first trimester. Accordingly, sharp or suction D&C ideally should be performed before 14 to 15 weeks' gestation.

The incidence of uterine perforation associated with elective abortion varies. Two important determinants are the skill of the physician and position of the uterus. Rates of perforation increase with a retroverted uterus and a less experienced surgeon. Much greater likelihood of perforation if the uterus is retroverted. Accidental uterine perforation usually is recognized when the instrument passes without resistance deep into the pelvis. Observation may be sufficient if the uterine perforation is small, such as when produced by a uterine sound or narrow dilator. Considerable intra-abdominal damage, however, can be caused by instrumentsâ€”especially suction and sharp curettesâ€”passed through a uterine defect into the peritoneal cavity (Keegan, 1982). Because unrecognized bowel injury can cause severe peritonitis and sepsis, laparoscopy or laparotomy to examine the abdominal contents is often the safest course of action in these cases (Kambiss, 2000).

Rarely, women may develop cervical incompetence or intrauterine adhesions following D&C. Those contemplating abortion should understand the potential for these rare but serious complications.

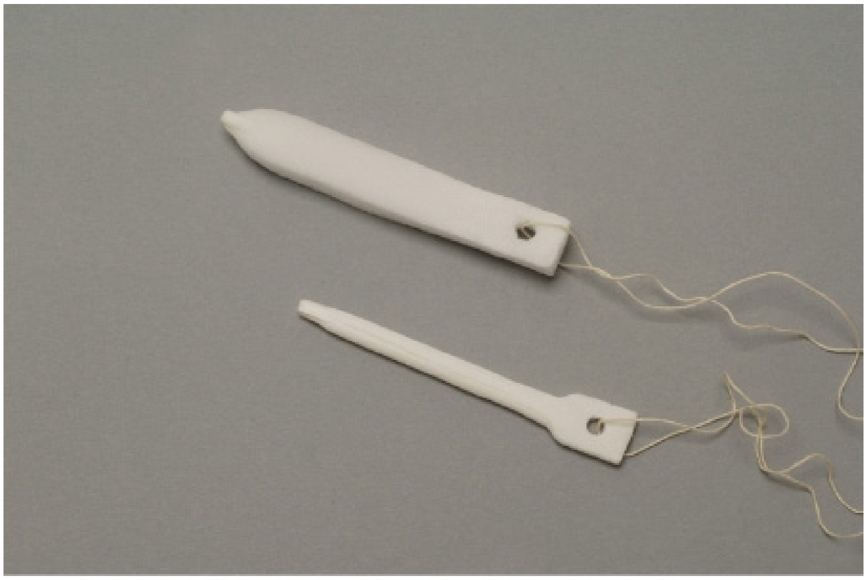
PATIENT PREPARATION

Suction D&C may be performed for cases of incomplete or inevitable abortion and require no cervical dilatation for procedure completion. However, other settings require manual dilatation of the cervical os with metal dilators, a procedural step closely associated with uterine perforation and patient discomfort. Therefore, to obviate this need, hygroscopic dilators may be placed in the endocervical canal to the level of the internal os to accomplish cervical dilatation.

Hygroscopic dilators draw water from cervical tissues and expand, which gradually dilates the cervix. One type of hygroscopic dilator originates from the stems of *Laminaria digitata* or *Laminaria japonica,* a brown seaweed. The stems are cut, peeled, shaped, dried, sterilized, and packaged according to their hydrated sizeâ€”small, 3 to 5 mm diameter; medium, 6 to 8 mm; and large, 8 to 10 mm. The strongly hygroscopic laminaria presumably act by drawing water from cervical proteoglycan complexes. The complexes dissociate and thereby allow the cervix to soften and dilate.

Another device available is the synthetic hygroscopic dilator, Lamicel, which is a similarly shaped polyvinyl alcohol polymer sponge impregnated with anhydrous magnesium sulfate (Fig. 41-17.1).

FIGURE 41-17.1

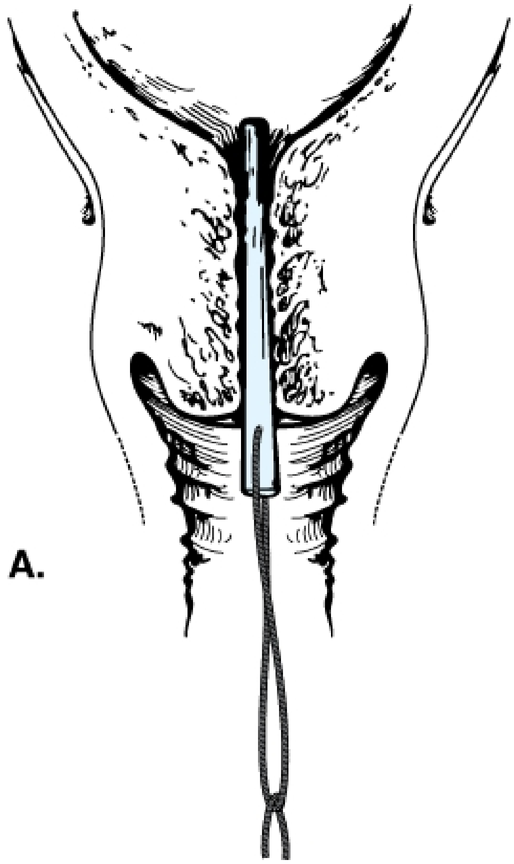


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Expanded laminaria (above) and dry laminaria (below).

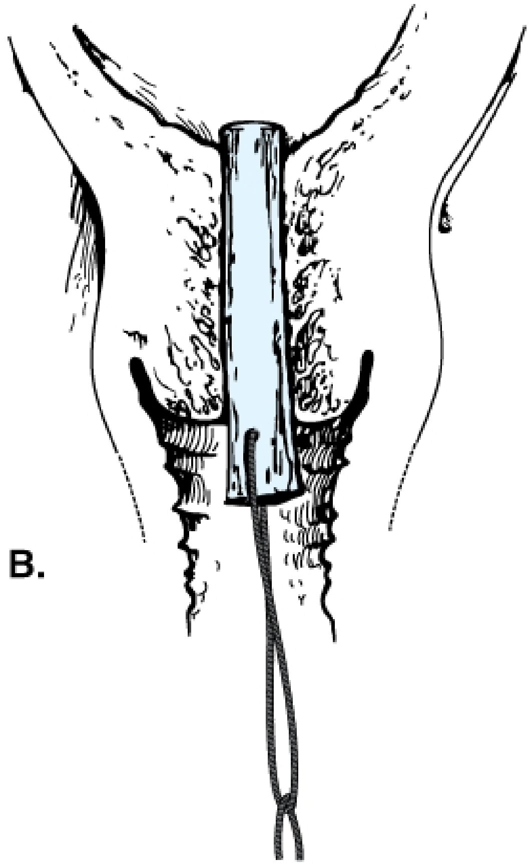
For placement of the dilators, the cervix is cleansed with povidone-iodine solution and is grasped anteriorly with a tenaculum. A laminaria of appropriate size then is inserted using a uterine packing forceps so that the tip rests at the level of the internal os (Fig. 41-17.2). After 4 to 6 hours, the laminaria will have swollen to dilate the cervix sufficiently and allow easier mechanical D&C. Cramping frequently accompanies expansion of the laminaria.

FIGURE 41-17.2



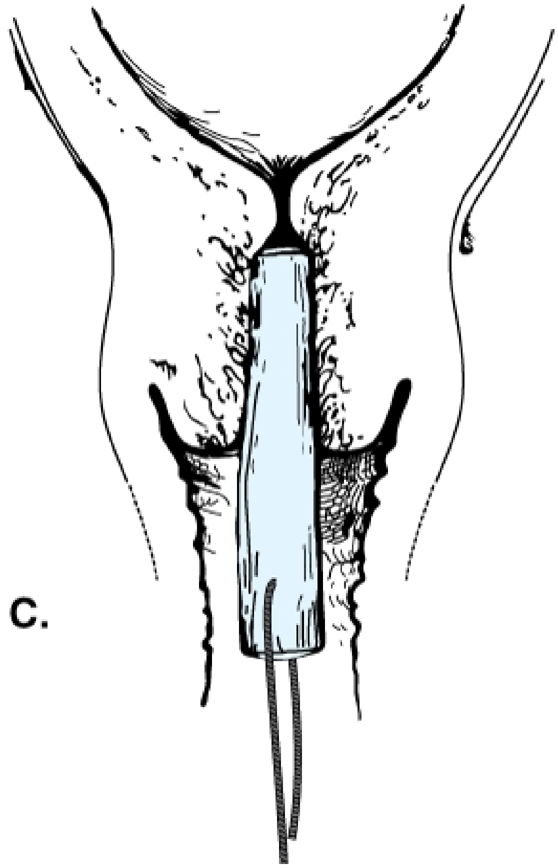
A.

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

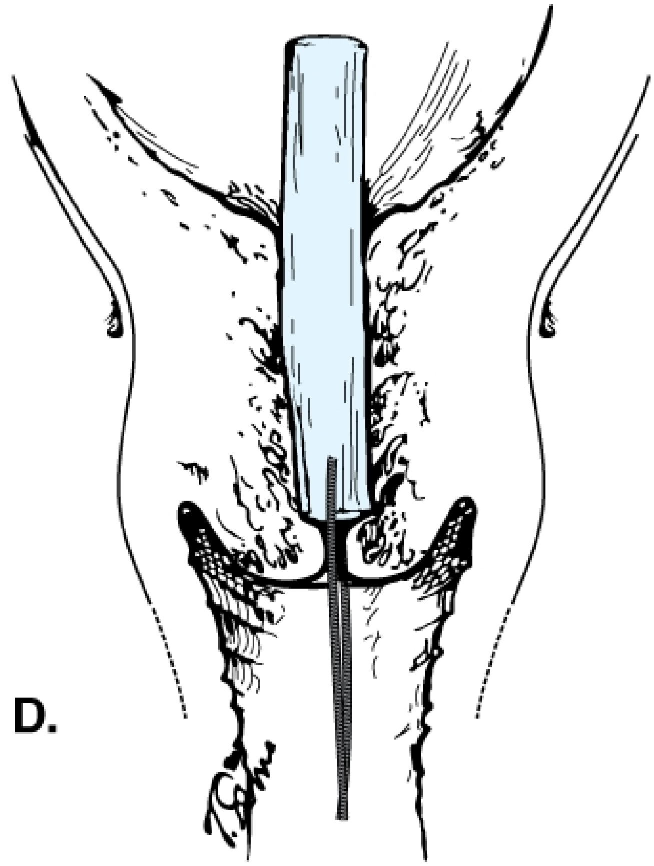


B.

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

A. Correct placement of laminaria. **B.** Expanded laminaria. **C.** Laminaria not inserted deeply enough to dilate the internal cervical os. **D.** Laminaria inserted too deeply past the internal cervical os.

In addition to hygroscopic dilators, various prostaglandin preparations have been investigated to soften the cervix for subsequent dilation. Misoprostol has been used effectively to induce uterine evacuation in properly selected patients. Studies investigating its use preoperatively to ease or obviate cervical dilatation, however, have not found it consistently effective in this clinical setting (Bunnasathiansri, 2004; Sharma, 2005).

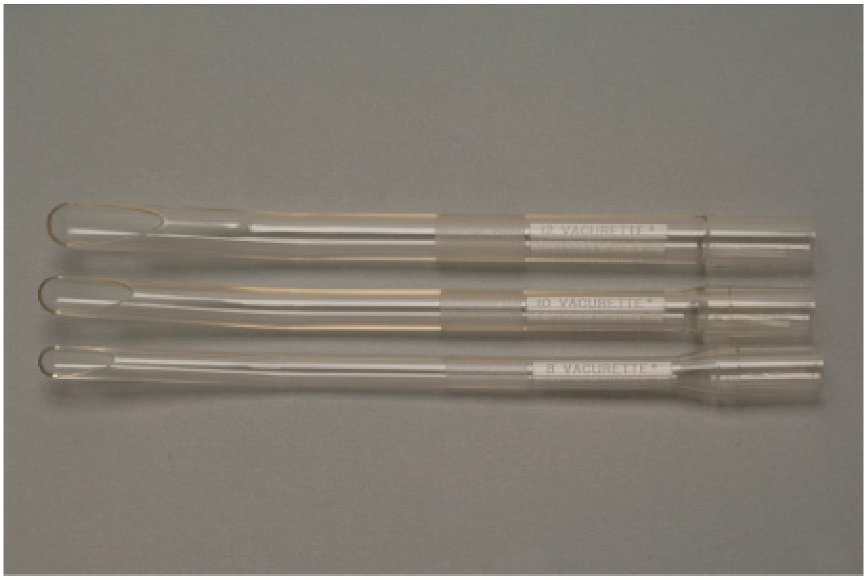
Antibiotic prophylaxis should be provided at the time of transcervical surgical abortion. Based on their review of 11 randomized trials, Sawaya and associates (1996) concluded that perioperative antibiotics decreased the risk of infection by 40 percent. Although no regimen appears superior to others, a convenient, inexpensive, and effective one is doxycycline 100 mg orally twice daily for 10 days.

Intraoperative

INSTRUMENTS

Suction D&C requires an electric suction unit; stiff, translucent, large-bore sterile suction tubing; and sterile Karman suction cannulas (Fig. 41-17.3). Plastic suction cannulas are available in varying diameters. Choosing the most appropriately sized cannula balances competing factors. Small cannulas risk retained intrauterine tissue postoperatively, whereas large cannulas risk cervical injury and more discomfort. For most first-trimester evacuations, a no. 8 to 12 Karman cannula is sufficient.

FIGURE 41-17.3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Karmen cannulas (sizes 4 to 12 mm).

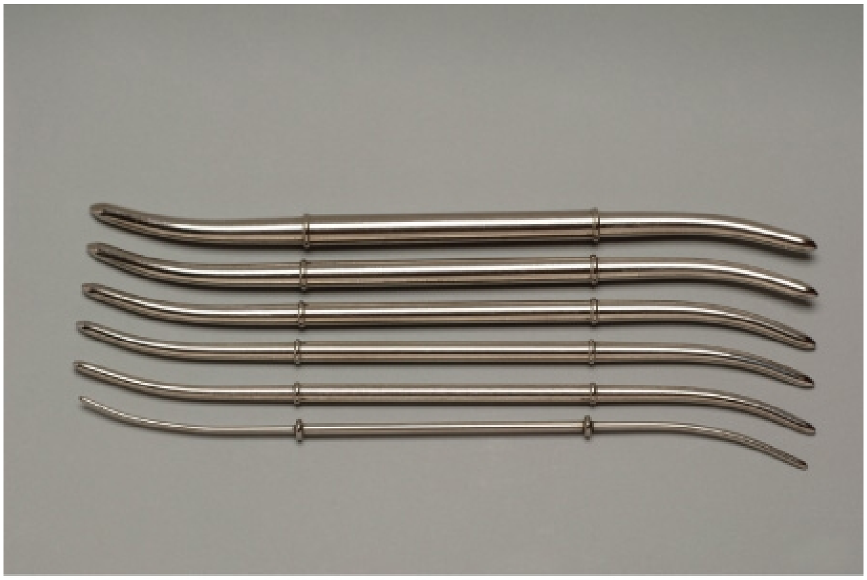
Surgical Steps

1. **Anesthesia and Patient Positioning.** In the absence of maternal systemic disease, abortion procedures do not require hospitalization. When abortion is performed outside a hospital setting, capabilities for cardiopulmonary resuscitation and for immediate transfer to a hospital must be available. Anesthesia or analgesia used may vary and includes general anesthesia, paracervical block plus intravenous sedation, or intravenous sedation alone. After delivery of anesthesia or analgesia, the patient is placed in dorsal lithotomy position, the bladder is drained, and the vulva and vagina are surgically prepped.

2. **Uterine Sounding.** A Simpson uterine sound is placed through the os and into the uterine cavity to measure the depth and inclination of the uterine cavity prior to dilatation (Fig. 41-16.1).

3. **Cervical Dilatation.** A Graves speculum is placed in the vagina to allow access to the cervix. In cases of incomplete or inevitable abortion, the cervical os already will be dilated. Alternatively, metal Pratt, Hegar, or Hank dilators (Fig. 41-17.4) of sequentially increasing diameter are placed through the external and internal os to gently dilate the cervix. The uterus is especially vulnerable to perforation during this step. For this reason, the metal dilator should be grasped as one would a pencil. The heel of the hand and fourth and fifth fingers rest on the perineum and buttock. Gentle pressure from only the thumb and first two fingers is used to push the dilator through the cervical os (Fig. 41-17.5).

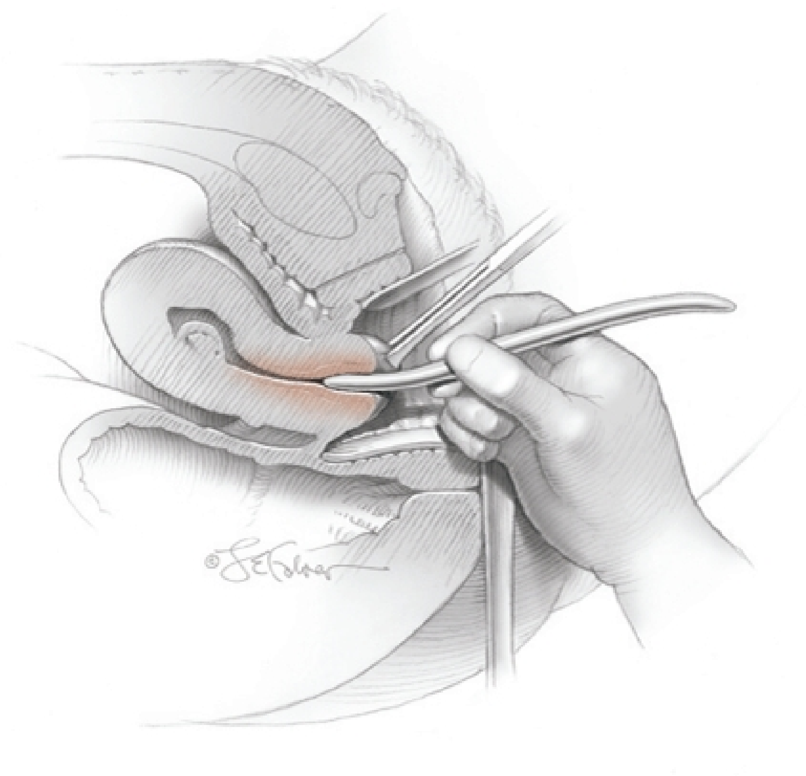
FIGURE 41-17.4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Pratt dilators of serially increasing diameter.

FIGURE 41-17.5



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Uterine dilatation.

4. **Uterine Evacuation.** The cannula is inserted through the open cervix and into the endometrial cavity. The suction unit is turned on, and uterine contents are removed. The suction cannula is moved toward the fundus and then back toward the os and is turned circumferentially to cover the entire surface of the uterine cavity.

   Tissue is collected in a container at the distal end of the tubing and is sent for pathologic evaluation to exclude hydatidiform mole. Occasionally, the Karman cannula may become obstructed with excess tissue. The suction unit is turned off prior to cannula removal. Once the cannula opening is cleared of obstructing tissue, it may be reinserted, and curettage completed.

5. **Sharp Curettage.** Although no more tissue is aspirated, a gentle sharp curettage should follow to remove any remaining placental or fetal fragments (see Section 41-6, Bartholin Gland Duct Incision and Drainage).

Postoperative

Recovery from suction D&C is typically fast and without complication. Patients may resume normal activities as they desire, but abstinence from intercourse usually is encouraged during the first week following surgery.

Ovulation may resume as early as 2 weeks after an early pregnancy ends. Therefore, if contraception is desired, methods should be initiated soon after abortion.

41-18 MYOMECTOMY

Myomectomy involves surgical removal of leiomyomas from their surrounding myometrium in an attempt to resolve abnormal

uterine bleeding, pelvic pain, and infertility. For these problems, approximately 500,000 myomectomies were performed in the United States from 1979 to 2001. Although surgeons performed hysterectomies at nearly 12 times this frequency within the same time period, myomectomy rates still nearly doubled (Burrows, 2005). Suggested causes for this increased rate of organ preservation include a delay in childbearing and concern about sexual dysfunction following hysterectomy (see Section 41-19, Hysterectomy).

Myomectomy typically requires laparotomy. However, laparoscopic excision may be performed by those with skills in laparoscopic suturing and suture ligation.

Preoperative

PATIENT EVALUATION

Because of their impact on preoperative and intraoperative planning, leiomyoma size, number, and location should be evaluated prior to surgery. Sonography, magnetic resonance (MR) imaging, or hysteroscopy may be used, as described in Chapter 9, Imaging. For example, submucous tumors are removed more easily hysteroscopically (see Section 41-37, Hysteroscopic Myomectomy), whereas intramural and serosal types typically require laparotomy. Leiomyomas may be small and buried within the myometrium. Therefore, accurate information as to leiomyoma number and location ensures complete excision. Lastly, multiple large tumors or those that are located in the broad ligament, near the cornua, or involving the cervix may increase the risk of conversion to hysterectomy, and patients should be so counseled.

CONSENT

Myomectomy has several risks, including significant bleeding and transfusion. Moreover, uncontrolled hemorrhage or extensive myometrial injury during tumor removal may force hysterectomy. Fortunately, rates of conversion to hysterectomy during myomectomy are low and range from 0 to 2 percent (Iverson, 1996; LaMorte, 1993; Sawin, 2000). Postoperatively, the risk of adhesion formation is significant, and leiomyomas can recur.

PATIENT PREPARATION

Hematologic Status

Menorrhagia is a common indication for myomectomy. As a result, many women who elect to undergo this surgery are anemic. In addition, significant intraoperative blood loss during myomectomy is possible (Iverson, 1996, LaMorte, 1993; Sawin, 2000).

For these reasons, attempts to resolve anemia and bleeding prior to surgery should be pursued. Toward this goal, oral iron therapy and gonadotropin-releasing hormone (GnRH) agonists may have benefits (see Chap. 9, GnRH Agonists). Benagiano and associates (1996) administered oral iron therapy alone or in combination with GnRH agonists and found the combination of the two to be significantly more effective in correcting preoperative anemia than either agonist use or iron therapy alone.

GnRH Agonists

In addition to control of preoperative menorrhagia, these agents have been shown to decrease uterine volume significantly after several months use (Benagiano, 1996; Friedman, 1991). As a result, decreased uterine size following treatment may allow a less invasive surgical procedure. For example, myomectomy may be completed through a smaller laparotomy incision or by laparoscopy or hysteroscopy (Crosignani, 1996; Lethaby, 2005; Mencaglia, 1993; Stovall, 1994). These agents also have been found to diminish leiomyoma vascularity and uterine blood flow (Matta, 1988; Reinsch, 1994). A final benefit may be adhesion prevention. Imai and associates (2003) noted lower rates of adhesion formation at second-look laparoscopy in women undergoing myomectomy who had received preoperative GnRH agonist therapy.

The use of preoperative GnRH agonists, however, also may have disadvantages. Within leiomyomas, GnRH agonists can incite hyaline or hydropic degeneration, which may obliterate the pseudocapsule connective tissue interface between the tumor and the myometrium. Such obliterated cleavage planes may lead to tedious and lengthy enucleation (Deligdish, 1997). Moreover, studies have shown higher rates of leiomyoma recurrence in women treated with GnRH agonists prior to myomectomy (Fedele, 1990; Vercellini, 2003). Leiomyomas treated with these agents may shrink in volume and be missed during surgical removal.

For these reasons, GnRH agonists should not be used routinely in all patients undergoing myomectomy. These can be

recommended for preoperative use in women with greatly enlarged uteri or preoperative anemia or in cases in which a decrease in uterine volume would allow a less invasive approach to leiomyoma removal (Broekmans, 1996; Lethaby, 2002).

Autologous Blood Donation

The risk of blood transfusion varies among studies and ranges from less than 5 percent to nearly 40 percent (Darwish, 2005; LaMorte, 1993; Sawin, 2000; Smith, 1990). For this reason, in cases involving large uteri, especially those with multiple leiomyomas, autologous blood donation may be considered. Similarly, "cell saver" blood scavenger and reuse techniques have been advocated (Yamada, 1997). Indication, benefits, and limitations to these forms of transfusion are discussed more fully in Chapter 40, Fluid Resuscitation and Blood Transfusion.

Preoperative Uterine Artery Embolization (UAE)

This is an angiographic interventional procedure that delivers obstructing particles via catheter into both uterine arteries (see Fig. 9-8). Vessels serving leiomyomas have a larger caliber and particles are preferentially directed to the tumors, sparing the surrounding myometrium. For this reason, UAE can be performed preoperatively to lower intraoperative blood losses during myomectomy.

Several disadvantages have been noted with UAE, including collateral infarction of adjacent tissue and complications in subsequent pregnancies (see Chap. 9, Uterine Artery Embolization). For these reasons, preoperative UAE may best be limited to women with large uteri in whom excess blood loss is expected and in those not seeking future pregnancy.

Antibiotic Prophylaxis

There are few studies addressing the benefits of preoperative antibiotic use prior to myomectomy. Iverson and co-workers (1996), in their analysis of 101 myomectomy patients, found that although 54 percent of patients received prophylaxis, infectious morbidity was not lower in these women than in those in whom antibiotics were not used.

In myomectomy performed for infertility, because of the potential for tubal adhesions associated with pelvic infection, antibiotic prophylaxis has been advocated (Chelmow, 2005). For patients in whom prophylaxis is planned, 1 g of a first- or second-generation cephalosporin is appropriate (Iverson, 1996, Periti, 1988, Sawin, 2000).

Bowel Preparation

Because of the low risk of bowel injury with this procedure, bowel preparation typically is not required unless extensive adhesions are anticipated. In contrast, because the risk of conversion to hysterectomy is present, vaginal preparation immediately prior to surgical draping is warranted.

Intraoperative

Surgical Steps

1. **Anesthesia and Patient Positioning.** Myomectomy performed through a laparotomy incision is typically an inpatient procedure performed under general or regional anesthesia. The patient is placed supine, the vagina and abdomen are surgically prepped, and a Foley catheter is placed.

2. **Abdominal Entry.** A Pfannenstiel incision typically is appropriate for uteri 14 weeks in size or smaller (see Section 41-2, Pfannenstiel Incision). Larger uteri usually require a vertical midline abdominal incision.

3. **Leiomyoma Identification.** Following abdominal entry, the surgeon should inspect the serosal surface to identify leiomyomas to be removed. Additionally, firm palpation of the myometrium before and during the surgery will help to identify intramural or submucous leiomyomas.

4. **Use of Uterine Tourniquet.** Tourniquets have been used for years to temporarily occlude blood flow through the uterine arteries. Because the uterus receives collateral flow through the ovarian arteries, some tourniquet techniques include occlusion of both uterine and ovarian vessels. To compress the uterine arteries, bilateral windows are created in the leaves of the broad ligament at the level of the internal cervical os. A Penrose drain or Foley catheter is threaded through the opening

to encircle the uterine isthmus. Once in place, the Penrose drain is tied or the ends of the Foley catheter are clamped to compress the uterine vessels. In combination with this, occlusion of the utero-ovarian ligaments or infundibulopelvic ligaments has been described (Delancey, 1992; Sapmaz, 2003; Taylor, 2005). Large, bulky uteri or those with leiomyomas in the broad ligament, however, may limit the use of tourniquets in some patients. In addition to temporary occlusion of the uterine arteries, permanent ligation of the uterine arteries has been described and shown to lower blood loss during myomectomy (Liu, 2004; Taylor, 2005).

5. **Use of Vasopressin.** 8-Arginine vasopressin (Pitressin, Parke Davis Co., Morris Plains, NJ) is a sterile aqueous solution of synthetic vasopressin. It is effective in limiting uterine blood loss during myomectomy because of its ability to cause vascular spasm and uterine muscle contraction. Compared with placebo, 8-arginine vasopressin injection has been shown to decrease blood loss significantly during myomectomy (Frederick, 1994). Compared with tourniquet techniques, 8-arginine vasopressin injection also has been associated with either comparable or less intraoperative blood loss and with equally low patient morbidity (Fletcher, 1996; Ginsburg, 1993). Moreover, Darwish and colleagues (2005) found lower rates of myometrial hematoma formation in those using 8-arginine vasopressin compared with those using tourniquet techniques.

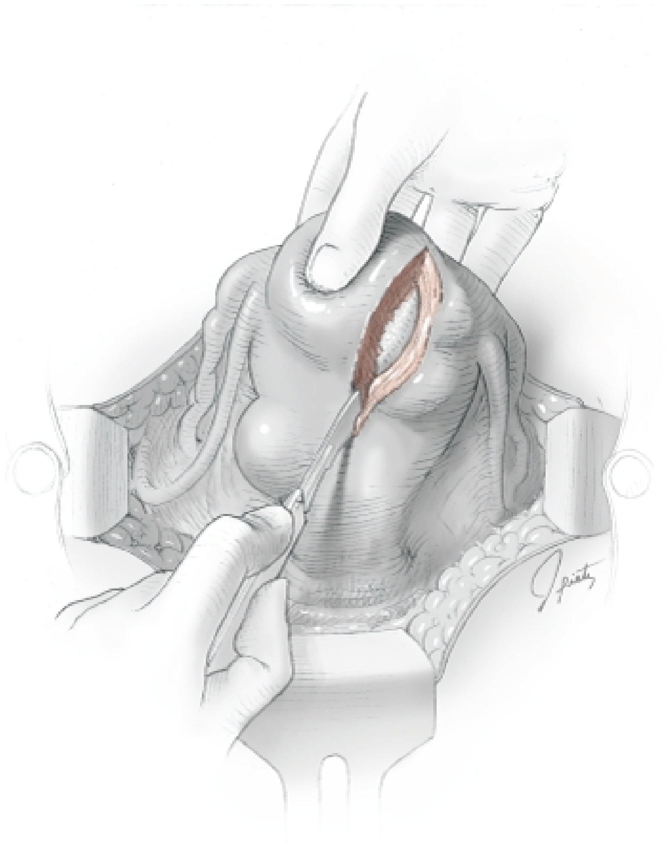
   Each vial of 8-arginine vasopressin is standardized to contain 20 pressor units/mL, and doses used for myomectomy range from 20 units diluted in 20 to 50 mL of saline (Bieber, 1998; Fletcher, 1996; Iverson, 1996). 8-Arginine vasopressin typically is injected along the planned serosal incision(s). The plasma half-life of this agent is 10 to 20 minutes. For this reason, injection of vasopressin should be discontinued 20 minutes prior to uterine repair to allow evaluation of bleeding from myometrial incisions (Hutchins, 1996).

   The main risks associated with local vasopressin injection result from inadvertent intravascular infiltration and include transient increases in blood pressure, bradycardia, atrioventricular block, and pulmonary edema (Deschamps, 2005; Tulandi, 1996). For these reasons, patients with a medical history of angina, myocardial infarction, cardiomyopathy, congestive heart failure, uncontrolled hypertension, migraine, asthma, and severe chronic obstructive pulmonary disease may not be candidates for 8-arginine vasopressin use.

6. **Serosal Incision.** Because of postoperative adhesion formation risks, surgeons should minimize the number of serosal incisions and attempt to place incisions on the anterior uterine wall. Tulandi and colleagues (1993) found that posterior wall incisions result in a 94-percent adhesion formation rate compared with a 55-percent rate for anterior incisions.

   For most patients, a midline vertical uterine incision allows removal of the greatest number of leiomyomas through the fewest incisions. The length should accommodate the approximate diameter of the largest tumor. The incision depth should afford access to all leiomyomas (Fig. 41-18.1). To reach lateral tumors, a surgeon may create lateral myometrial incisions within the initial central incision (see Fig. 41-18.4). However at times, separate incision may be required to excise tumors from these locations.

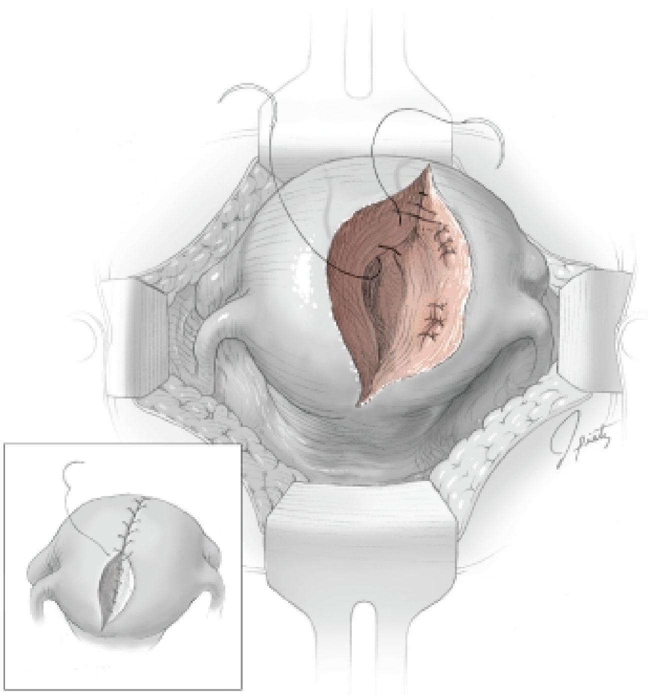
FIGURE 41-18.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Uterine incision.

FIGURE 41-18.4

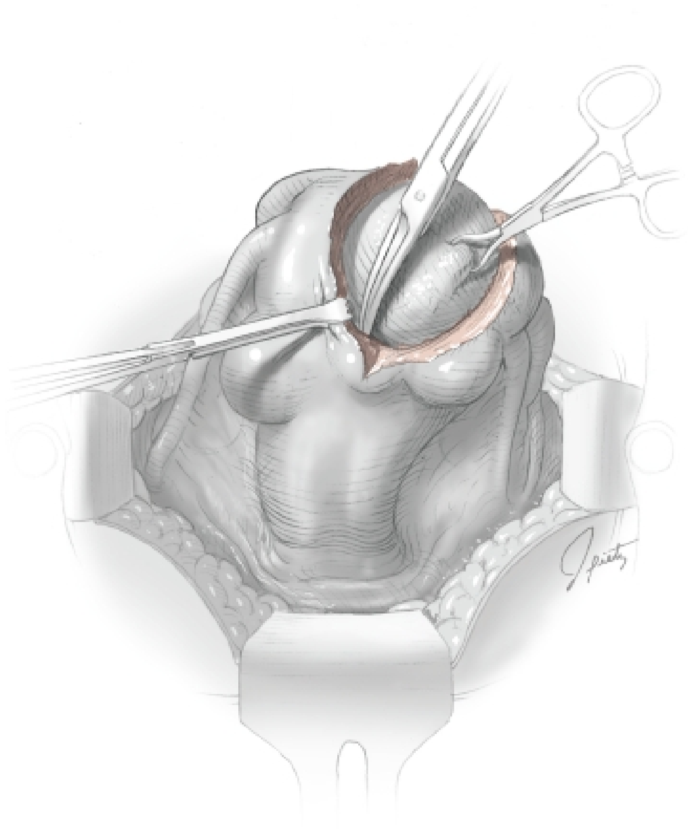


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Uterine incision closure.

7. **Tumor Enucleation.** The first leiomyoma is grasped with a Lahey or single-toothed tenaculum (Fig. 41-18.2). Alternatively, a leiomyoma screw also can be use to achieve tissue traction and create tissue tension between the myometrium and leiomyoma. Sharp and blunt dissection of the pseudocapsule surrounding the leiomyoma frees the tumor from the adjacent myometrium.

FIGURE 41-18.2

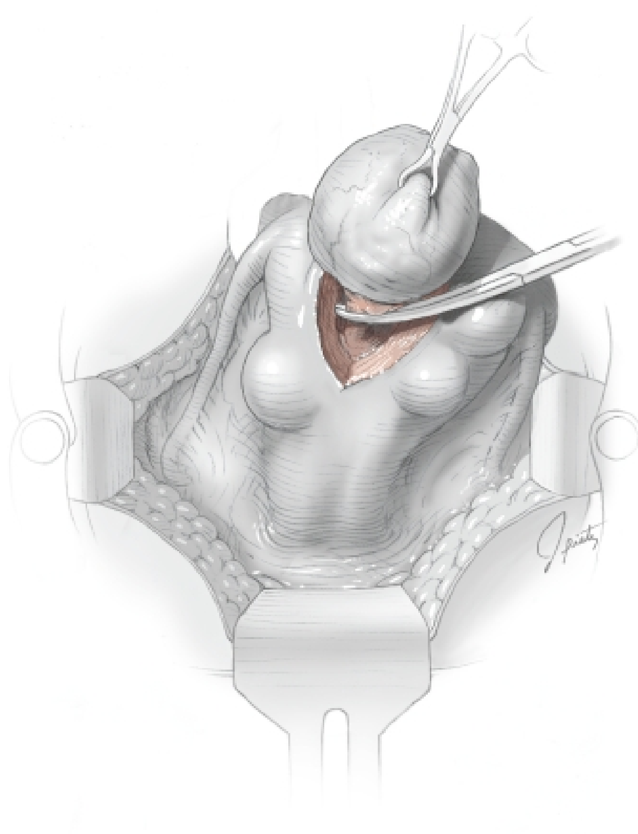


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Tumor enucleation.

8. **Bleeding.** Hemorrhage during myomectomy develops primarily during tumor enucleation and is correlated positively with preoperative uterine size, total weight of leiomyomas removed, and operating time (Ginsburg, 1993). Approximately two to four main arteries feed each leiomyoma and enter the tumor at unpredictable sites (see Fig. 9-2). For this reason, surgeons must watch for these vessels, ligate them prior to transection when possible, and be ready to grasp them immediately with hemostats for ligation or fulgaration if they are lacerated during tumor excision (Fig. 41-18.3).

FIGURE 41-18.3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Vessel ligation.

9. **Myometrial Incision.** Smaller internal incisions into the myometrium may be required to excise all leiomyomas. If the endometrial cavity is entered, it should be closed with a running suture of 4-0 or 5-0 delayed-absorbable suture.

10. **Myometrial Closure.** Following removal of all tumors, redundant serosa may be excised. Smaller internal myometrial incisions are closed first with delayed-absorbable suture (Fig. 41-18.4). The myometrium then is closed in layers to improve hemostasis and prevent hematoma formation. A gauge of sufficient strength to prevent breakage during muscle approximation is selected, typically 0 to 2-0.

11. **Serosal Closure.** Closure of the serosal incision using a running baseball suture with 4-0 or 5-0 monofilament delayed-absorbable suture may help to limit adhesion formation (Fig. 41-18.4, inset). In addition, absorbable adhesion barriers such as Interceed (Ethicon, Piscataway, NJ) have been shown to reduce the incidence of adhesion formation following myomectomy (Farquhar, 2000). Mettler and co-workers (2004) in a German trial showed a 65-percent reduction in adhesions following myomectomy using SprayGel (Confluent Surgical, Waltham, MA), an adhesion barrier.

Postoperative

Following abdominal myomectomy, postoperative care follows that for any major abdominal surgery. Hospitalization typically varies from 1 to 4 days, and return of normal bowel function and febrile morbidity usually dictate this course. Postoperative activity in

general can be individualized, although vigorous exercise usually is delayed until 4 to 6 weeks after surgery.

FEVER

Febrile morbidity of greater than 38.0Â°C is a common event following myomectomy (Darwish, 2005; Iverson, 1996; LaMorte, 1993). Purported causes include atelectasis, myometrial incisional hematomas, and factors released with myometrial destruction. Although fever is common following myomectomy, pelvic infection is not. For example, LaMorte and colleagues (1993) noted only a 2-percent rate of pelvic infection in their analysis of 128 myomectomy patients.

SUBSEQUENT PREGNANCY

There are no clear guidelines as to the timing of pregnancy attempts following myomectomy. Darwish and colleagues (2005) performed sonographic examinations on 169 patients following myomectomy. Following myometrial indicators, they concluded that wound healing usually is completed within 3 months.

41-19 HYSTERECTOMY

Hysterectomy is one of the most frequently performed gynecologic procedures, with approximately 600,000 women undergoing this procedure annually in the United States (Farquhar, 2002; Kozak, 2002). The reasons for hysterectomy are varied and include both benign and malignant etiologies. Of benign indications, symptomatic leiomyomas and pelvic organ prolapse are the most frequent, although abnormal bleeding, endometriosis, chronic pain, and premalignant neoplasia are also relatively common.

Preoperative

PATIENT EVALUATION

A spectrum of tests may be required to reach the preoperative diagnosis. These tests vary depending on the clinical setting and are discussed within the respective chapters covering those etiologies. Prior to hysterectomy, however, all patients require Pap smear screening, and abnormal findings require evaluation for cervical cancer prior to surgery (see Chap. 29, Differential Diagnosis and Evaluation of Cervical Lesions). Similarly, women at risk for endometrial cancer and whose indication includes abnormal bleeding typically are also screened before surgery (see Chap. 8, Endometrial Biopsy).

HYSTERECTOMY APPROACH

Hysterectomy may be completed using an abdominal, vaginal, or laparoscopic approach, and selection is influenced by many factors. For example, physical properties of the uterus and pelvis, surgical indications, presence or absence of adnexal pathology, surgical risks, costs, hospitalization and recovery length, and anticipated postoperative quality of life are all weighed once hysterectomy is planned. All three approaches are used commonly, and each carries distinct advantages and disadvantages.

Abdominal Hysterectomy

Most uteri in the United States are removed through an abdominal incision. Either a transverse or a vertical incision may be selected depending on the clinical setting (see Sections 41-1, Midline Vertical Incision and Section 41-2, Pfannenstiel Incision) (Farquhar, 2002). Abdominal hysterectomy allows the greatest ability to manipulate pelvic organs and thus is preferred if large pelvic organs or extensive adhesions are anticipated. In addition, an abdominal approach affords access to the ovaries if oophorectomy is desired, to the space of Retzius when concurrent urogynecologic procedures are planned, or to the upper abdomen for cancer staging. Abdominal hysterectomy typically requires less operating time than laparoscopic hysterectomy and requires no advanced laparoscopic instrumentation or expertise (Falcone, 1999).

However, abdominal hysterectomy is associated with longer patient recovery and hospital stays, increased incisional pain, and greater risk of postoperative febrile morbidity and wound infection (Johns, 1995; Johnson, 2005; Marana, 1999). Additionally, compared with a vaginal approach, abdominal hysterectomy is associated with greater risk of transfusion and ureteral injury but lower rates of postoperative bleeding and bladder injury (Harris, 1996).

Vaginal Hysterectomy

This approach usually is chosen by surgeons if pelvic organs are small, extensive adhesions are not anticipated, no significant

adnexal pathology is expected, and some degree of pelvic organ prolapse is present. When this approach is compared with abdominal hysterectomy, women more often benefit from faster recovery and from reduced hospital stays, costs, and postoperative pain.

Laparoscopic Hysterectomy

This approach typically is selected for women if pelvic organs are small, extensive adhesions are not expected, uterine descensus is poor, and surgeons are skilled in laparoscopic techniques. Although patient recovery, hospital stays, and postoperative pain scores are comparable with those of vaginal hysterectomy, this approach allows greater visualization and access to the abdomen and pelvis. This may be advantageous if oophorectomy is planned or if bleeding or minor adhesive disease is encountered. However, laparoscopy typically requires longer operating times and more expensive equipment. In addition, it has been associated with greater rates of ureteral injury (as high as 14 percent) than either abdominal (0.4 percent) or vaginal hysterectomy (0.2 percent) (Harkki-Siren, 1997a). Laparoscopically assisted vaginal hysterectomy may be considered in those cases in which one or more factors are amenable to laparoscopic manipulation and thus, once corrected, allow hysterectomy to be completed vaginally.

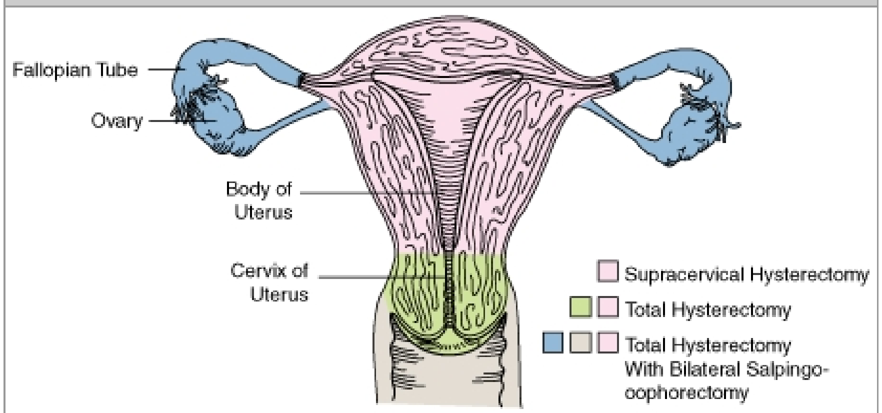
Approach Selection

In sum, if all factors are equal, vaginal hysterectomy should be considered. However, when large pelvic organs, risk of associated malignancy, extensive adhesions, or poor uterine descensus is present, either abdominal or laparoscopic hysterectomy may be required. Of note, surgical expertise is factored into the decision and heavily dictates the approach selected.

Total versus Supracervical Hysterectomy

Prior to hysterectomy, the decision to remove the cervix concurrently is typically discussed with the patient. Hysterectomy may include removal of the uterus and cervix, termed *total hysterectomy,* or may involve only the uterine corpus, called *supracervical hysterectomy* (Fig. 41-19.1). The term s*ubtotal hysterectomy* refers to the supracervical type but is not preferred usage.

FIGURE 41-19.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Hysterectomy classification.

During the latter half of the twentieth century, most hysterectomies performed were total hysterectomies. The supracervical technique was reserved for patients in whom excision of the cervix risked increased bleeding, surrounding organ damage, or increased operating time.

However, suggested improvement in urinary symptoms and preservation of sexual function have been attributed to cervical conservation, and a trend began in the 1990s toward supracervical hysterectomy (Kilkku, 1983, 1985). Proponents suggest that the cervix provides an important stabilizing function for pelvic support and that the Frankenhauser nerve plexus can be disrupted during total hysterectomy, causing bladder, bowel, or sexual dysfunction. Additionally, advocates argue that this approach decreases surrounding pelvic organ injury and operating times, especially during a laparoscopic approach to hysterectomy

(Baggish, 2005).

Randomized studies, however, have failed to support differences in sexual or urinary function following total abdominal or supracervical hysterectomy (Gimbel, 2005a; Kupperman, 2004; Roussis, 2004; Thakar, 2002). In addition, Learman and co-workers (2003) found no statistically significant differences between the two in surgical complications and clinical outcomes during 2 years of surveillance. In addition, chronic bleeding may follow supracervical hysterectomy. Between 10 and 20 percent of women still will note vaginal bleeding, presumably from retained isthmic endometrium following hysterectomy. Most of these cases end in trachelectomy (Section 41-23, Trachelectomy) (Gimbel, 2005b; Okaro, 2001). Procedures that ablate or core out the endocervical canal may help to prevent this complication (Ewen, 1994; Jenkins, 2004).

Critics of supracervical hysterectomy also have noted the persistent risk for cancer in the conserved stump. However, the risk for cervical cancer in these women is comparable with that in those without hysterectomy, and the prognosis for cervical stump cancer mirrors that in those with a uterus (Hannoun-Levi, 1997; Hellstrom, 2001; Silva, 2004).

In sum, abdominal supracervical hysterectomy offers no distinct advantage over total abdominal hysterectomy, and the risks of persistent bleeding following surgery may deter many women and clinicians from its use.

CONSENT

Hysterectomy for most women is a safe and effective treatment that typically leads to an improved postoperative quality of life and psychological outcome (Hartmann, 2004; Thakar, 2004). However, pelvic organs may be injured during surgery. Vascular, bladder, and ureteral injury are cited most commonly. Accordingly, risks of blood loss and transfusion usually are discussed with a patient before surgery.

Concurrent Bilateral Oophorectomy

Hysterectomy is performed frequently with other surgical procedures. Pelvic reconstructive surgeries and bilateral salpingo-oophorectomy are among the most common.

Ovaries are removed prophylactically in approximately half of hysterectomy cases performed for benign indications. In women younger than 40 years, ovaries typically are conserved because the number of years of expected hormone production is great. In those older than 50 years, bilateral oophorectomy is typical. However, for those in their forties, the decision to remove ovaries prophylactically is controversial.

Proponents of prophylactic oophorectomy argue that the procedure eliminates future ovarian cancer risk and is estimated to prevent 1,000 new cases of ovarian cancer each year (American College of Obstetricians and Gynecologists, 1999). Secondly, the duration of significant ovarian estrogen production following hysterectomy for many is shortened. For example, Siddle and co-workers (1987) noted the mean age of ovarian failure in a group undergoing hysterectomy was 45 years. This was significantly lower than the mean age of 49 years in a control group not receiving surgery. In addition, women with retained ovaries may require future surgery for subsequent benign ovarian disease, and this risk ranges from 1 to 5 percent (Bukovsky, 1988; Zalel, 1997).

However, in those declining oophorectomy, the risk for ovarian cancer still is decreased by 40 to 50 percent by hysterectomy alone (Chiaffarino, 2005; Green, 1997). Additional disadvantages to oophorectomy include long-term effects of hypoestrogenism, such as risks for osteoporosis and coronary artery disease. Parker and colleagues (2005) noted an increased rate of survival to 80 years in women after hysterectomy at ages 50 to 54 years with ovarian conservation (62 percent) compared with those electing oophorectomy without estrogen-replacement therapy (ERT) (54 percent). Although these rates became nearly equal in those electing oophorectomy and then receiving postoperative ERT, concerns regarding ERT compliance have been noted (see Chap. 22) (Speroff, 1991). Castelo-Branco and co-workers (1999) found that after 5 years following hysterectomy and oophorectomy, only a third of women still continued their ERT. Most stopped because of cancer concerns.

In addition to the loss of estrogen, ovarian androgen production is lost. However, its importance in later life has not been entirely delineated (Olive, 2005).

PATIENT PREPARATION

Postoperative vaginal cuff cellulitis and urinary tract infection are risks following hysterectomy. For this reason, patients typically receive antibiotic prophylaxis with either a first- or second-generation cephalosporin (Hemsell, 2001). Alternatively, metronidazole or tinidazole may be used (see Table 39-7). The risk of bowel injury with hysterectomy is low. Accordingly, for most women, an enema administered prior to surgery to evacuate the rectum is sufficient. A more extensive preparation may be indicated if extensive pelvic adhesive disease is anticipated.

Intraoperative

Surgical Steps

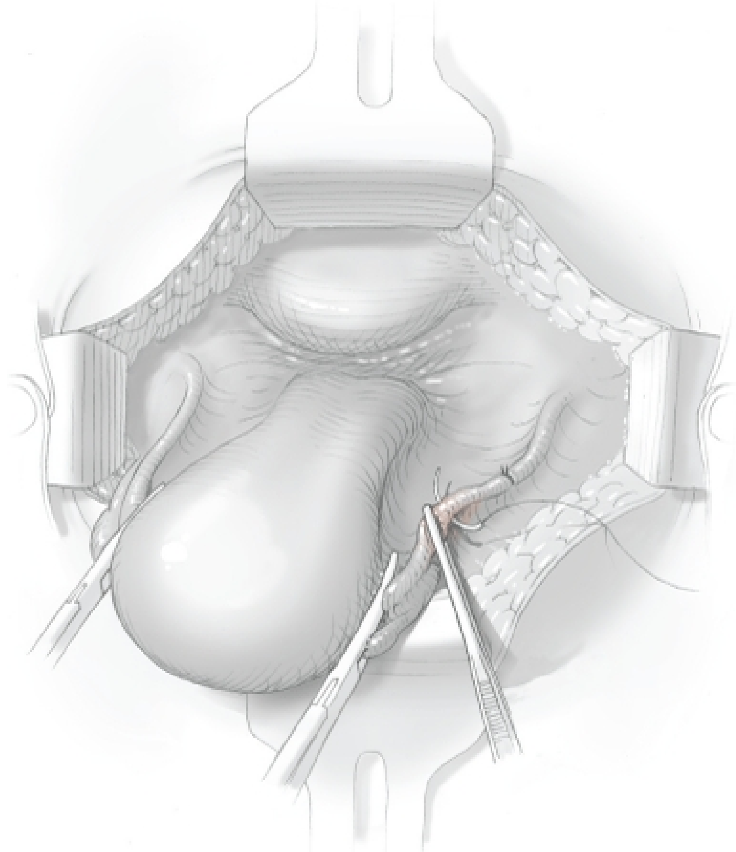
1. **Anesthesia and Patient Positioning.** Abdominal hysterectomy typically is performed under general anesthesia, although regional anesthesia also may be used. The patient is positioned supine, a Foley catheter is placed, and the abdomen and vagina are prepped for surgery.

2. **Abdominal Entry.** Either a transverse or a vertical incision may be used for hysterectomy, and clinical factors influence selection (see Sections 41-1, Midline Vertical Incision and 41-2, Pfannenstiel Incision).

3. **Exposure.** Following entry into the abdomen, a self-retaining retractor such as an O'Connor-O'Sullivan or Balfour retractor is placed. The pelvis and abdomen are explored visually and manually, and the bowel is packed from the operating field. The uterus is grasped and elevated from the pelvis. If extensive adhesions are present, normal anatomic relationships are restored to aid surgery. Hysterectomy may be performed by one surgeon, but commonly two surgeons are present, with each typically operating on his or her side of the uterus.

4. **Round Ligament Transection.** Curved Kelly clamps are placed bilaterally across each fallopian tube and utero-ovarian ligament immediately lateral to the uterus (Fig. 41-19.2). Attention is directed to one of the round ligaments, where midsection division is planned. A transfixing suture using 0-gauge delayed-absorbable suture is placed about 1 cm proximally and another suture 1 cm distally to this planned division. These sutures are held by hemostats and are directed upward and outward to create tension along the interposed segment of round ligament. The round ligament is cut, and this incision is directed inferiorly into the first 1 to 2 cm of the broad ligament.

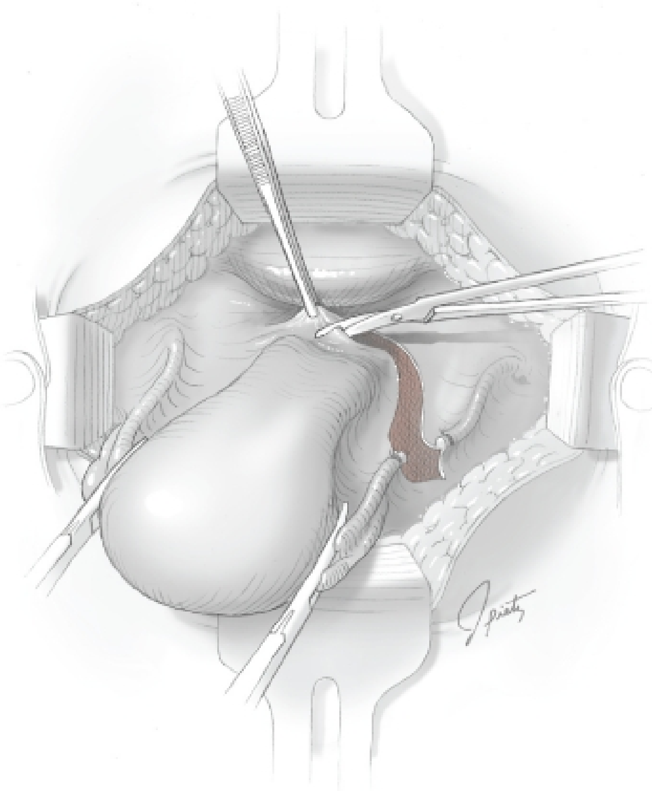
FIGURE 41-19.2



Round ligament transection.

5. **Broad Ligament Leaves.** With this action, the broad ligament separates to create anterior and posterior leaves, and between them, gauzy areolar connective tissue is seen. The leading medial and lateral edges of the anterior leaf are grasped with smooth atraumatic forceps. Tension on these edges is directed upward and outward. The tented anterior leaf then is incised sharply, with the line of incision curving inferiorly and medially to the level of the vesicouterine fold (Fig. 41-19.3). Similarly, the posterior leaf of the broad ligament is opened. The incision extends inferomedially toward the uterosacral ligaments. At this point, it is advantageous to identify the ureters, particularly before any tissue clamps are placed.

FIGURE 41-19.3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

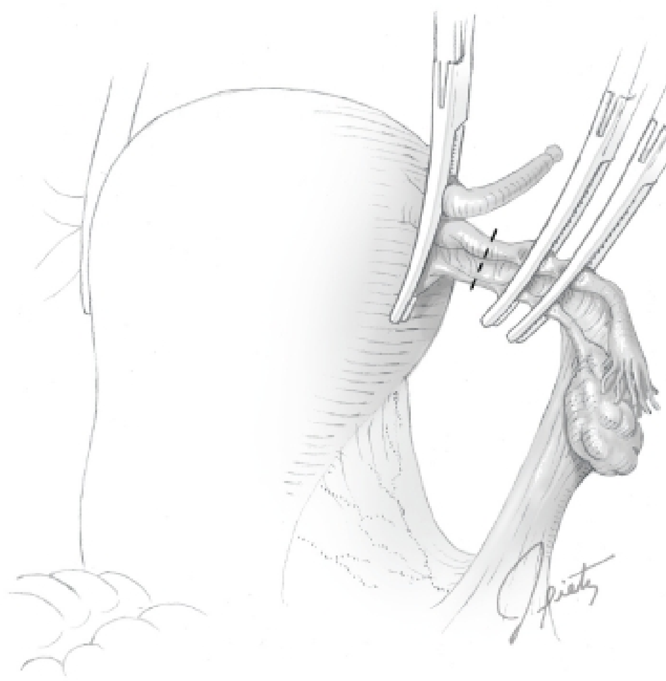
Anterior leaf opened.

6. **Ovarian Conservation.** Attention now may be directed to the adnexa. With the leaves of the broad ligament now open, if adnexa are to be preserved, the surgeon's index finger can be curved under the fallopian tube and utero-ovarian ligament (Fig. 41-19.4).

   One Kelly clamp was already placed at the beginning of surgery across the fallopian tube and utero-ovarian ligament and lies proximal to the surgeon's finger. Two Heaney or other appropriate clamps then are placed lateral to the finger, with each clamp arc directed toward the uterus (Fig. 41-19.4).

   The surgeon's finger is removed, and the intervening segment of fallopian tube and utero-ovarian ligament is incised between the medial Heaney clamp and Kelly clamp. A free tie of 0-gauge delayed-absorbable suture is placed around the more lateral of the two Heaney clamps. As the knot of this suture is tied securely, the lateral of these two clamps is removed. A transfixing suture then is placed around the remaining Heaney clamp. This suture is placed above and distal to the first free tie. As the knot is cinched in place, the Heaney clamp is removed. The Kelly clamp is left in place. The adnexa is now freed from the uterus.

FIGURE 41-19.4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Ovarian conservation.

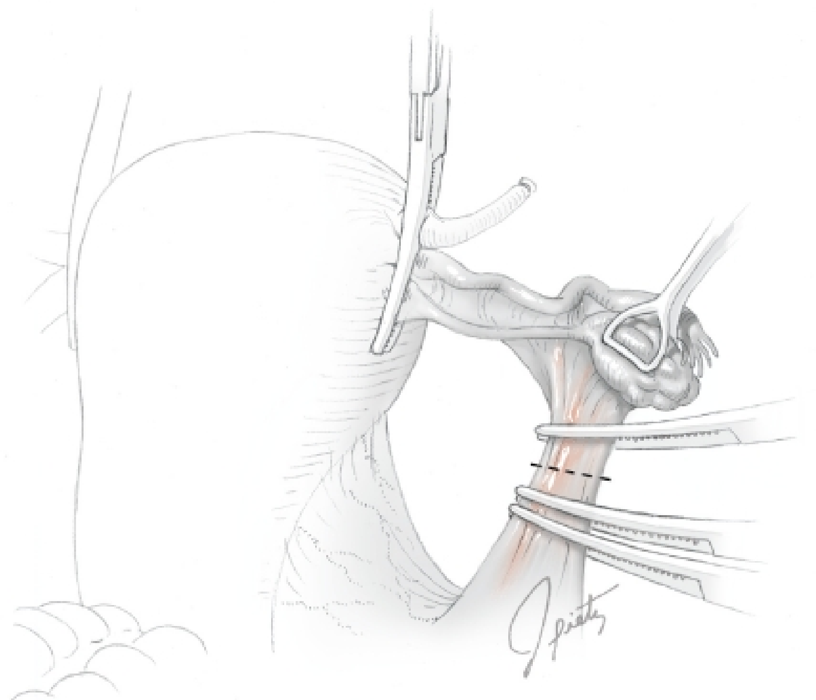
7. **Oophorectomy.** If the adnexa are to be removed, the tube and ovary are grasped with a Babcock clamp and elevated away from the infundibulopelvic (IP) ligament (Fig. 41-19.5). The peritoneum lateral to this ligament is incised, and this incision is extended cephalad and laterally. The peritoneum medial to the IP ligament was incised earlier as part of the posterior leaf of the broad ligament.

   With the IP ligament now isolated, curved Heaney clamps can be placed around this ligament. As with the utero-ovarian ligaments, two clamps are placed proximal to the planned site of incision, and one clamp is placed distally. All arcs of these curved clamps are directed toward the site of planned incision.

   Once the clamps have been placed, the IP ligament is transected. Ligation of the IP is carried out as in step 9. A free-tie 0-gauge delayed-absorbable suture is placed around the more proximal of the two Heaney clamps. As the knot of this suture is tied securely, the proximal clamp is removed. A transfixing suture then is placed around the remaining Heaney clamp. This suture is placed above and distal to the first free tie. As the knot is cinched in place, the remaining Heaney clamp is removed.

   The adnexum is now freed from the pelvic sidewall and its increased mobility may obstruct surgery. For this reason, the adnexa can be tied to the Kelly clamp located on the utero-ovarian ligament.

FIGURE 41-19.5



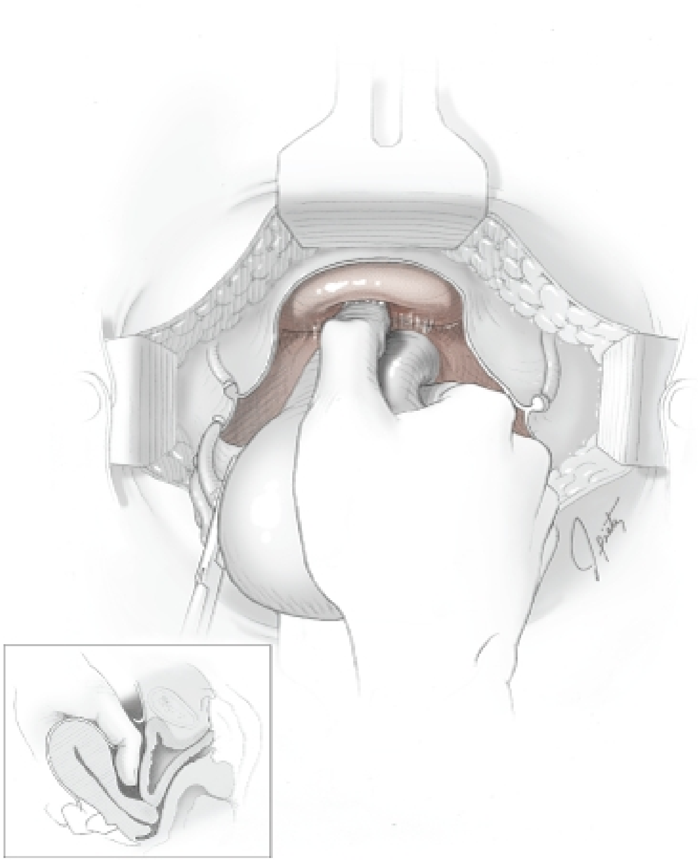
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Oophorectomy.

8. **Bladder Flap.** Attention next is turned to the bladder. The peritoneum that connects the superior edge of the bladder to the uterine isthmus was cut when the anterior leaf of the broad ligament was opened. Only loose areolar connective tissue joins the posterior surface of the bladder and anterior surface of the uterine isthmus and cervix. As a result, a hand can be wrapped around the uterus and a thumb used to exert gentle pressure under the bladder and against the uterine surface inferiorly toward the vagina. Countertension on the uterus is created by pulling upward on the Kelly clamps previously placed at the cornua. Similarly, a sponge stick can be used to create this pressure. In this fashion, the bladder can be separated from the underlying lower uterine segment and cervix (Fig. 41-19.6).

   Alternatively, some patients may have scar tissue connecting the posterior surface of the bladder to the anterior uterine surface. In this instance, sharp dissection with Metzenbaum scissors may be required to detach the bladder from the isthmus and cervix.

FIGURE 41-19.6



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

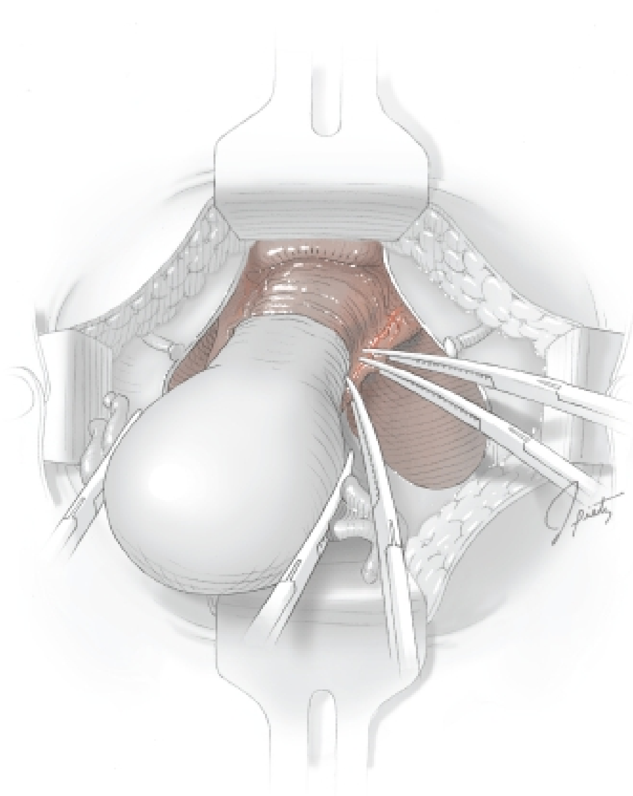
Bladder flap dissection.

9. **Uterine Arteries.** Next, the uterine arteries are identified along the lateral aspects of the uterus at the level of the isthmus. Excess connective tissue surrounds these vessels and is grasped with fine, smooth forceps. The connective tissue is retracted gently laterally and away from the vessels. Curved Metzenbaum scissors incise this tissue beginning superiorly and proceeding inferiorly. The technique is often referred to as *skeletonizing* and removes excess tissue from around vessels prior to their ligation.

   Two curved Heaney clamps are placed on the uterine vessels inferiorly to the planned site of vessel transection. These clamp tips are placed horizontally across the vertical axis of the uterine vessels (Fig. 41-19.7). A third curved clamp is placed above the planned incision. Its tip crosses the vessels at an approximate 45-degree angle. The uterine vessels are then sharply transected.

   A simple stitch of 0-gauge delayed-absorbable suture is placed below the lowest clamp's tip, and the suture ends are wrapped to the heel of the clamp. As the knot is cinched, the middle of the three clamps is opened and then closed immediately. The lowest of the three then is removed. A simple stitch then is placed above the first suture and below the middle clamp. As the knot is cinched, this clamp is removed. The upper clamp is left in place to prevent vessel bleeding from the rich collateral uterine circulation.

FIGURE 41-19.7



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

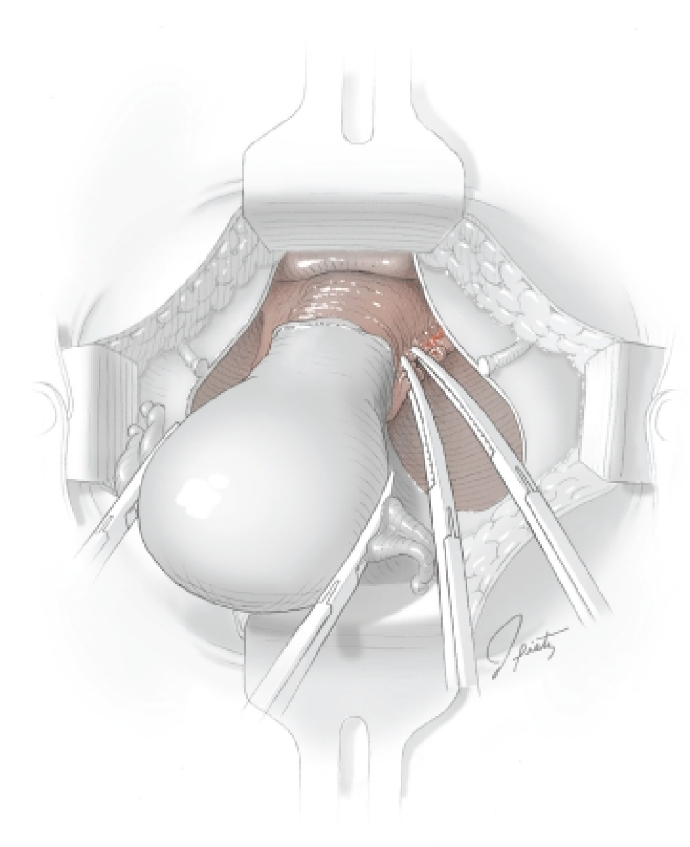
Uterine artery ligation.

10. **Fundal Amputation.** After bilateral ligation of the uterine arteries, if the uterus is large and bulky, the uterine fundus may be severed sharply from the isthmus and cervix. After removal of the corpus, a single-toothed Kocher clamps can be placed on the anterior and posterior walls of the uterine isthmus to elevate the cervix.

11. **Cardinal Ligament Incision.** These ligaments lie lateral to the uterus and are inferior to the uterine vessels. A straight Heaney clamp is used to clamp the cardinal ligament (Fig. 41-19.8). As the Heaney clamp initially grasps the ligament, it is oriented parallel to the lateral side of the uterus. As the clamp is slowly closed, it is angled approximately 45 degrees from the vertical axis of the uterus. A second clamp may be placed medial to the first. A scalpel is used to transect the portion of the cardinal ligament held between the clamps. A transfixing suture of 0-gauge delayed-absorbable suture is placed below the clamp, the knot is cinched, and the clamp removed. The medial Heaney clamp, if used, is left in place to prevent bleeding.

    Because of the vertical length and vascularity of the cardinal ligament, it may be necessary to repeat step 11. In this manner, the cardinal ligament is ligated, from its superior to inferior extent, using a series of clamping and suturing events down the lateral aspect of the uterus and lateral aspect of the upper vaginal vault.

FIGURE 41-19.8

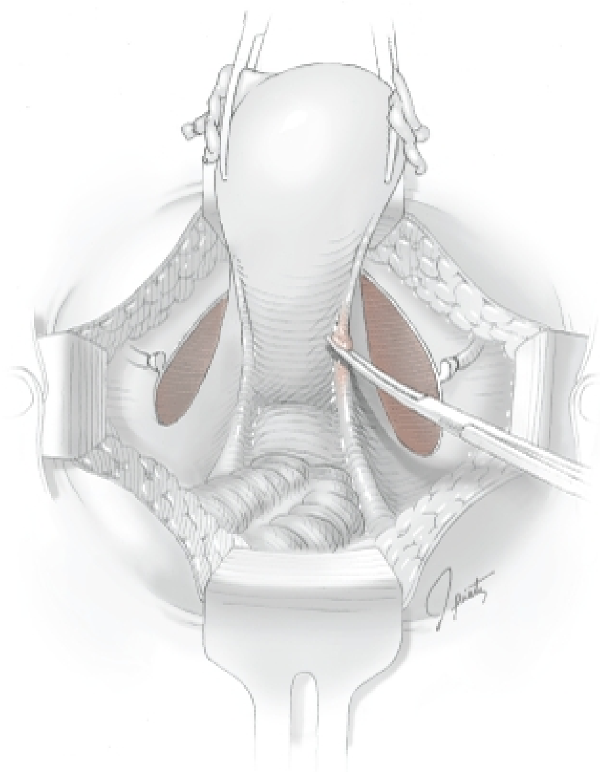


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Cardinal ligament transection.

12. **Uterosacral Ligament Transection.** At this point, attention is directed to the posterior aspect of the uterus and to the uterosacral ligaments (Fig. 41-19.9). Upward traction is exerted by the Kelly clamps placed at the uterine cornua. Each ligament is grasped with a straight Heaney clamp close to its uterine attachment. Importantly, because of the close proximity of the ureter, these clamps are placed as close to the uterus as possible. The ligament is severed medial to the clamp, a transfixing suture is placed, and the clamp is removed.

FIGURE 41-19.9

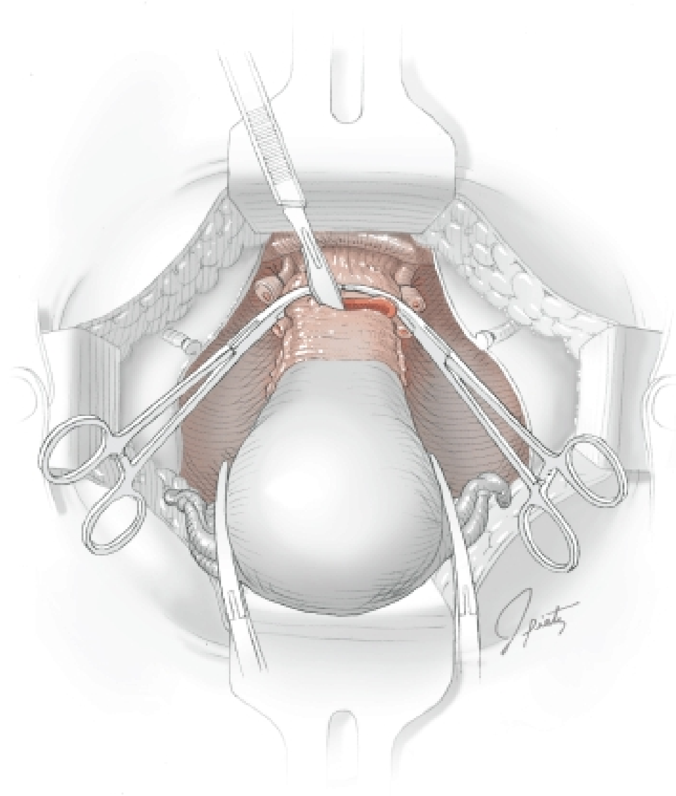


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Uterosacral ligament transection.

13. **Vaginal Entry.** At this point the surgeon's hand may palpate through the anterior and posterior vaginal walls to identify the most inferior level of the cervix. Here, curved Heaney clamps are used grasp and bring together the anterior and posterior vaginal walls at the point just below the cervix (Fig. 41-19.10).

FIGURE 41-19.10



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

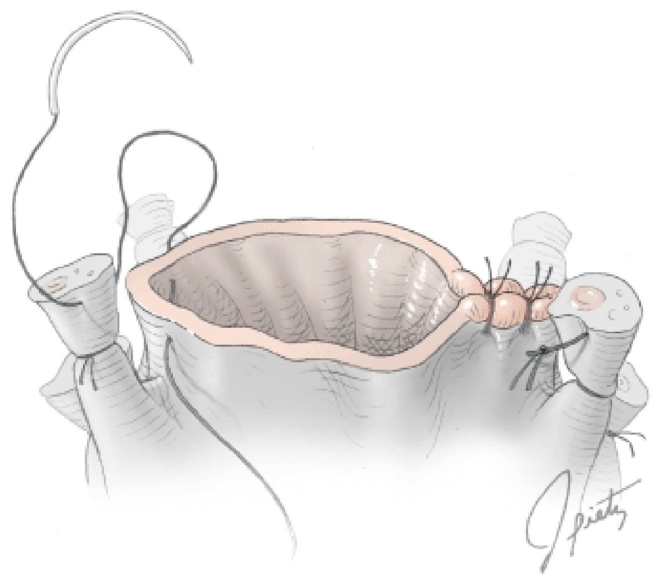
Uterine excision.

14. **Removal of the Uterus.** The vaginal tissue above these clamps then is incised, and vaginal tissue extending between these two clamps then is cut with knife or Mayo scissors. This procedure frees the uterus from the pelvis. Transfixing sutures are placed below the Heaney clamps, and the clamps are removed.

15. **Vaginal Cuff Closure.** A long length of 0-gauge delayed-absorbable suture is used to join together the uterosacral ligament pedicle and the vaginal apex pedicle on the right (Fig. 41-19.11). A knot will cinch these together. A similar bundle is tied together on the left of the vaginal apex. This bilateral joining of the vaginal apex to the uterosacral ligaments helps to prevent vaginal cuff prolapse following surgery.

    The short ends of the sutures used to bind these pedicles are grasped with hemostats. These hemostat are directed upward and laterally to create tension along the vaginal cuff. The anterior cut edge of the vagina then is reapproximated to the posterior cut vaginal edge with several figure-of-eight sutures using 0-gauge delayed-absorbable suture. The lateral elevating sutures then are cut.

FIGURE 41-19.11



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Vaginal cuff closure.

16. **Wound Closure.** The abdominal incision is closed as described in Sections 41-1, Midline Vertical Incision and 41-2, Pfannenstiel Incision.

Postoperative

Following abdominal hysterectomy, postoperative care follows that for any major abdominal surgery. Hospitalization typically varies from 1 to 4 days, and return of normal bowel function and febrile morbidity usually dictate this course. Postoperative activity in general can be individualized, although intercourse usually is delayed until 4 to 6 weeks after surgery to allow time for vaginal cuff healing.

Febrile morbidity is common following abdominal hysterectomy and exceeds that seen with vaginal or laparoscopic approaches (Peifert, 2004). Frequently, fever is unexplained, but pelvic infections are common. Additionally, abdominal wound infection, urinary tract infection, and pneumonia should be considered (see Fig. 39-6). Because of the high rate of unexplained fever, which resolves spontaneously, observation for 24 to 48 hours for mild temperature elevations is reasonable. Alternatively, in those at higher risk of infection, a second-generation cephalosporin may be administered. Additional testing, including transvaginal sonography or computed tomographic scanning, may be indicated if a pelvic hematoma or abscess is suspected.

41-20 VAGINAL HYSTERECTOMY

In general, vaginal hysterectomy offers short patient recovery, operating times, and hospitalization as well as decreased surgical morbidity. Ideally, it is used when pelvic organs are small, some degree of uterine descensus is present, and access to the upper abdomen is not required. Similarly, this approach typically is not selected in those with a contracted pelvis or significant pelvic adhesions.

Preoperative

Patient evaluation, consent, and patient preparation are similar to those for abdominal hysterectomy (see Section 41-19, Hysterectomy).

Intraoperative

Surgical Steps

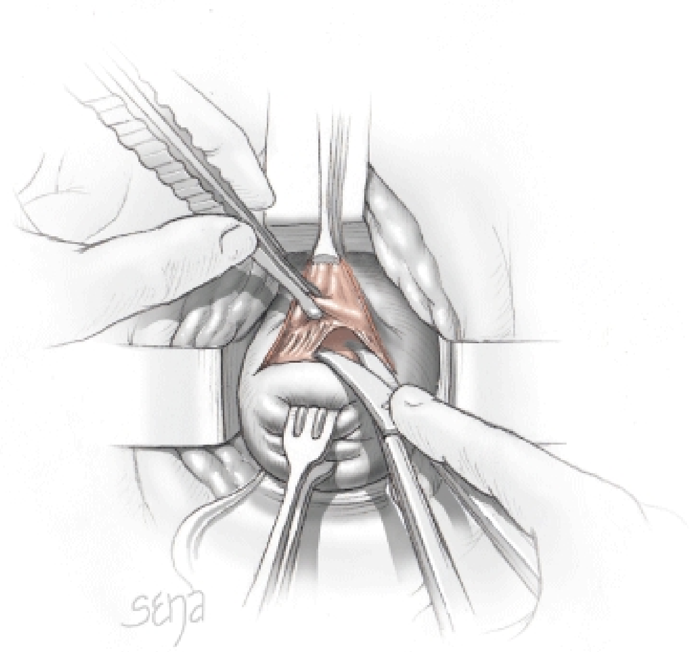
1. **Anesthesia and Patient Positioning.** After adequate general or regional anesthesia is administered, the patient is placed in high or standard dorsal lithotomy position (see Chap. 40, Dorsal Lithotomy). The vagina is surgically prepped, and a Foley catheter is placed. A right-angle or other suitable retractor is placed along the anterior vaginal wall, whereas a weighted vaginal speculum is placed posteriorly.

2. **Vaginal Wall Incision.** A Lahey thyroid clamp is used to grasp both the anterior and posterior cervical lips and close them together. Between 10 and 15 mL of a dilute saline solution containing vasopressin (20 units diluted in 20 mL of saline) or 0.5-percent lidocaine and epinephrine (1:200,000 dilution) is injected circumferentially beneath the mucosa at a level above the cervicovaginal junction but below the inferior margin of the bladder. The margin of the bladder is identified as a crease in the overlying vaginal epithelium. This margin can be accentuated by in-and-out displacement of the cervix (Sheth, 2005). Injection of vasocontrictors decreases bleeding during dissection and aids in defining tissue planes. The vaginal wall above the cervix then is circumcised. To avoid dissection into the cervix, this incision is kept at a depth superficial to the pubocervical fascia.

3. **Anterior Peritoneal Entry.** The anterior vaginal wall is grasped and elevated with an Allis clamp. Additional, tension is created by outward traction on the Lahey thyroid clamp. This traction will reveal fibrous bands connecting the bladder and cervix. With surgical gauze covering the index finger, the surgeon pushes downward and cephalad against the cervix to bluntly dissect through these fibers and move the bladder anteriorly. This motion is continued until the vesicouterine fold is reached. In patients in whom these cervicovesical fibrous bands are dense, sharp dissection may be required to avoid blunt cystotomy by the surgeons's finger (Fig. 41-20.1).

   The vesicouterine fold can be seen as a transverse white line across the anterior cervix. Palpation reveals two thin smooth layers of peritoneum slipping against one another (Fig. 41-20.2). The vesicouterine fold is grasped and elevated to place this peritoneal layer on tension. The peritoneum then is incised (Fig. 41-20.3). An index finger explores the opening to confirm peritoneal entry and palpate for any unanticipated pathology. The anterior retractor then is repositioned with its distal blade entering the peritoneal cavity and elevating the bladder.

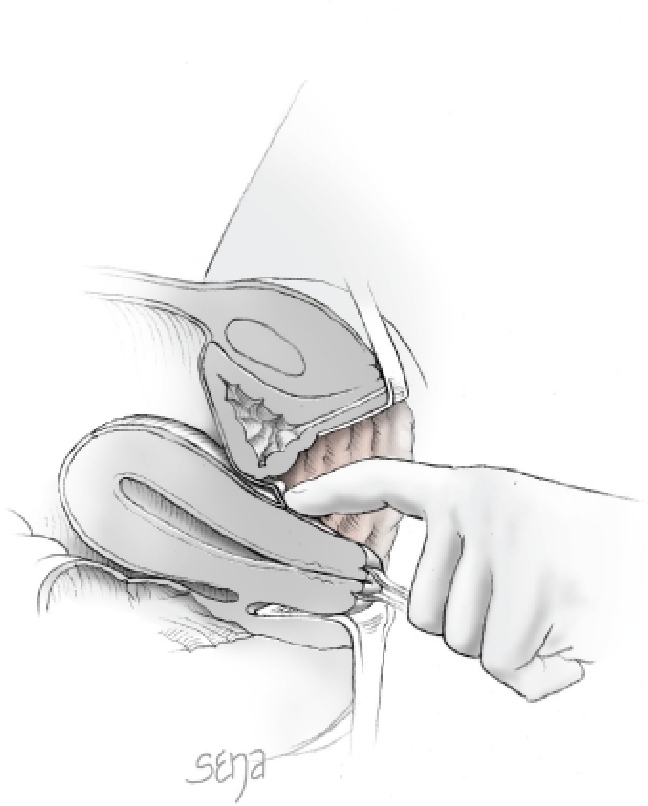
FIGURE 41-20.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Sharp dissection of vaginal mucosa.

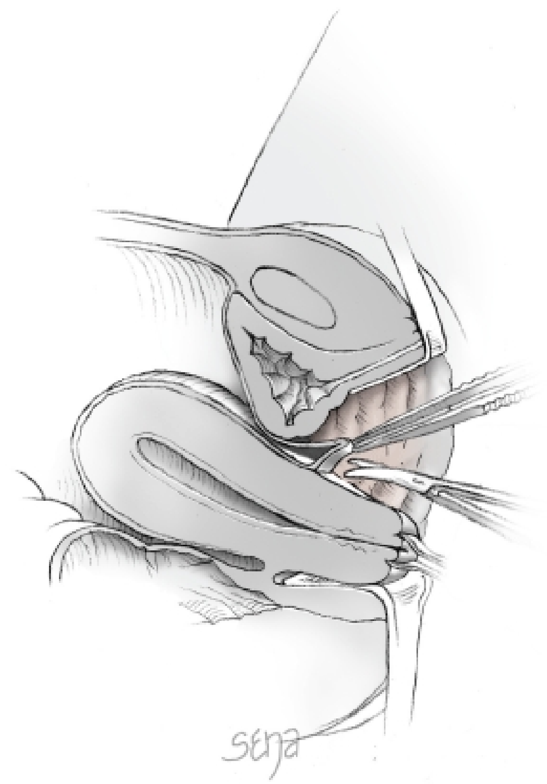
FIGURE 41-20.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Vesicouterine fold identification.

FIGURE 41-20.3

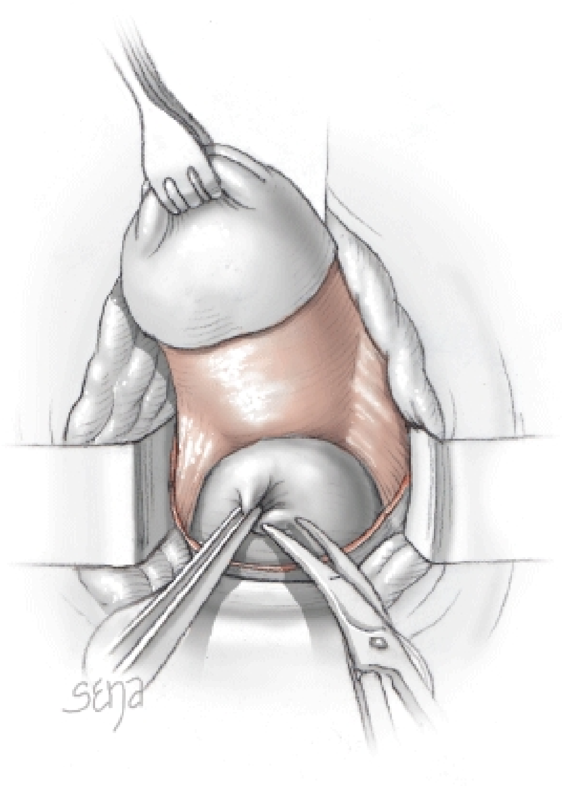


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Vesicouterine fold incision.

4. **Posterior Entry.** The Lahey thyroid clamp and cervix are lifted anteriorly to expose the posterior vaginal vault, and an Allis clamp is placed on the incised edge of the posterior vaginal wall. The Allis clamp is pulled downward to create tension across the exposed posterior peritoneum. The posterior vaginal vault is cut with curved Mayo scissors, and the Douglas cul-de-sac is entered (Fig. 41-20.4). The posterior peritoneum is affixed centrally to the posterior vaginal wall incision with a single stitch of delayed-absorbable suture. This approximation will assist with closure of the peritoneum at the procedure's end. The short, weighted vaginal speculum is replaced by one with a longer blade, which enters the cul-de-sac.

FIGURE 41-20.4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Entry into the cul-de-sac of Douglas.

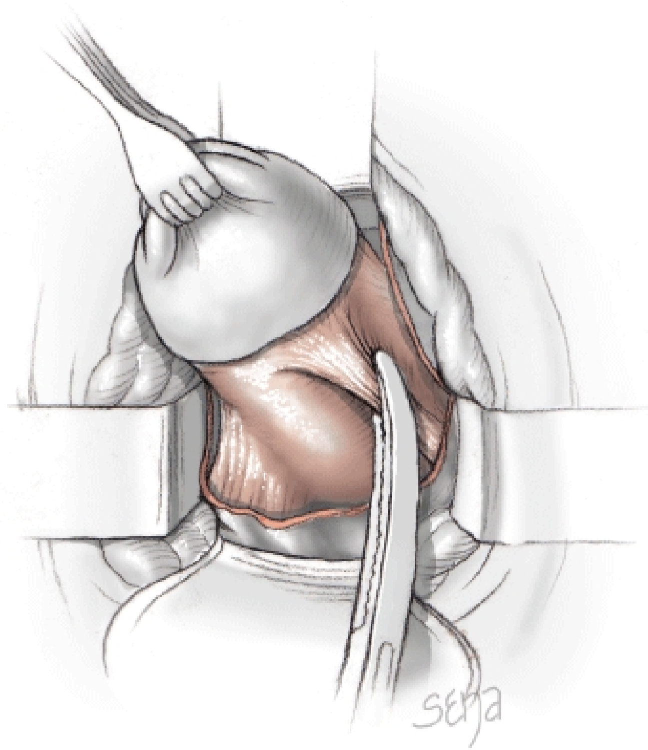
5. **Transection of Uterosacral and Cardinal Ligaments.** Outward traction on the Lahey thyroid clamp pulls the supporting uterine ligaments into view. Such traction on the cervix aids in preventing ureteral injury.

   The uterosacral ligament is identified, clamped with a curved Heaney clamp, transected, and ligated with 0-gauge delayed-absorbable suture using a transfixing stitch (Fig. 41-20.5).

   After ligation of the uterosacral ligaments, the cardinal ligaments similarly are clamped, cut, and sutured (Fig. 41-20.6). When the anterior jaw of the Heaney clamp is positioned around the cardinal ligament, the anterior peritoneal edge is pulled downward and incorporated into the pedicle.

   The uterosacral and cardinal ligaments may be isolated, clamped, and ligated individually or in combination depending on the size of each. Once the knots of these pedicles are secured, the suture ends are not cut but rather are held by hemostats. These will be sutured later to the vaginal cuff to aid in long-term vaginal support.

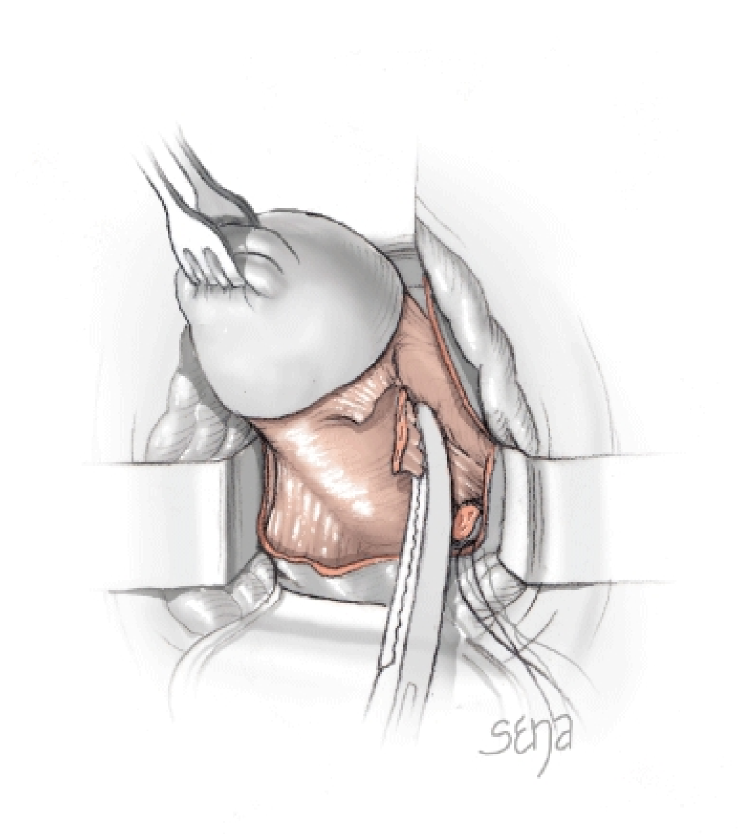
FIGURE 41-20.5



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Uterosacral ligament transection.

FIGURE 41-20.6



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

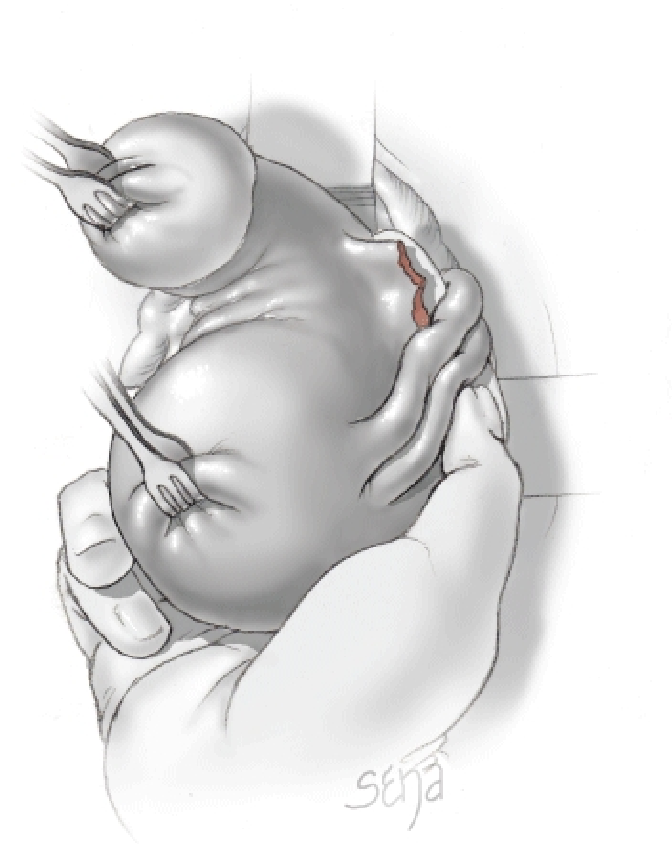
Cardinal ligament transection.

6. **Uterine Arteries.** The uterine arteries are identified and serially clamped with two curved Heaney clamps. A simple suture is placed behind the proximal clamp and is secured as this clamp is removed. A second suture is then placed behind the distal clamp.

7. **Utero-ovarian and Round Ligaments.** If the uterus is small and descensus adequate, two curved Heaney clamps may be placed in tandem across the utero-ovarian and round ligaments and fallopian tubes. Each pedicle is doubly ligated with a simple suture first placed medially. A transfixing stitch is then placed distally and held by hemostat.

   Alternatively, if the uterus is larger, the uterine corpus may be delivered through either the anterior or posterior colpotomy incision to expose these ligaments (Fig. 41-20.7). To deliver the fundus, either fingers or a tenaculum can be used to pull the fundus into the vagina.

FIGURE 41-20.7



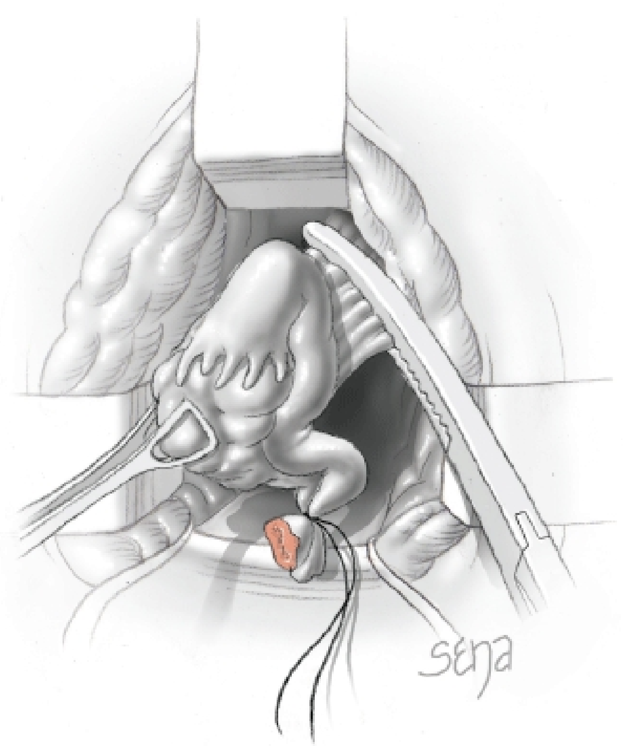
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Utero-ovarian and round ligaments transection.

8. **Morcellation.** In some cases, a uterine fundus may be too large to deliver, and debulking of the uterus may be required. This can be done by enucleating individual large leiomyomas or by cervix-to-fundus central coring using scissors or scalpel. Once the bulk has been diminished, Heaney clamps may be placed around the utero-ovarian ligaments as described in step 7.

9. **Oophorectomy.** If removal of the ovaries is desired, the adnexa is grasped with a Babock clamp and gently pulled toward the incision. An index finger is wrapped around the infundibulopelvic (IP) ligament to isolate it from surrounding structures. The IP ligament is clamped and ligated similarly to the utero-ovarian pedicle. The ends of its final transfixing suture are held by hemostat (Fig. 41-20.8).

FIGURE 41-20.8

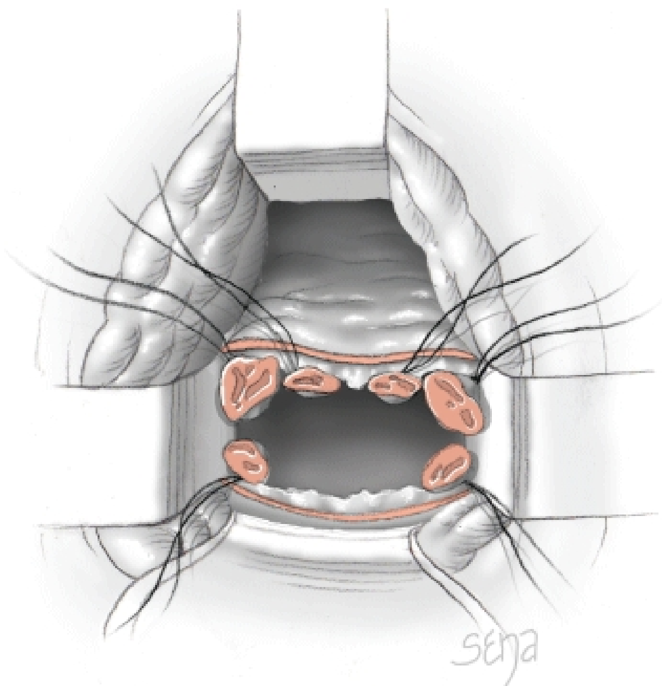


Oophorectomy.

10. **Evaluation of Hemostasis.** Following removal of the uterus, the surgical pedicles are inspected for bleeding. Electrosurgical coagulation or individual figure-of-eight sutures typically will control bleeding. If hemostasis is adequate, sutures to the IP ligament are cut. At this juncture, if an enterocoele repair is planned, it is performed.

11. **Vaginal Cuff Closure.** The peritoneum is closed in a purse-string manner using 2-0 delayed-absorbable suture. Next, a suspensory suture may be included in which the cardinal or uterosacral or both ligaments are sutured to the lateral vaginal cuff on each side to improve final suspension and support for the vaginal vault (Figs. 41-20.9 and 41-20.10). This is repeated on the left. The vaginal wall incision is closed left to right with interrupted or continuous running sutures of 0-gauge delayed-absorbable material.

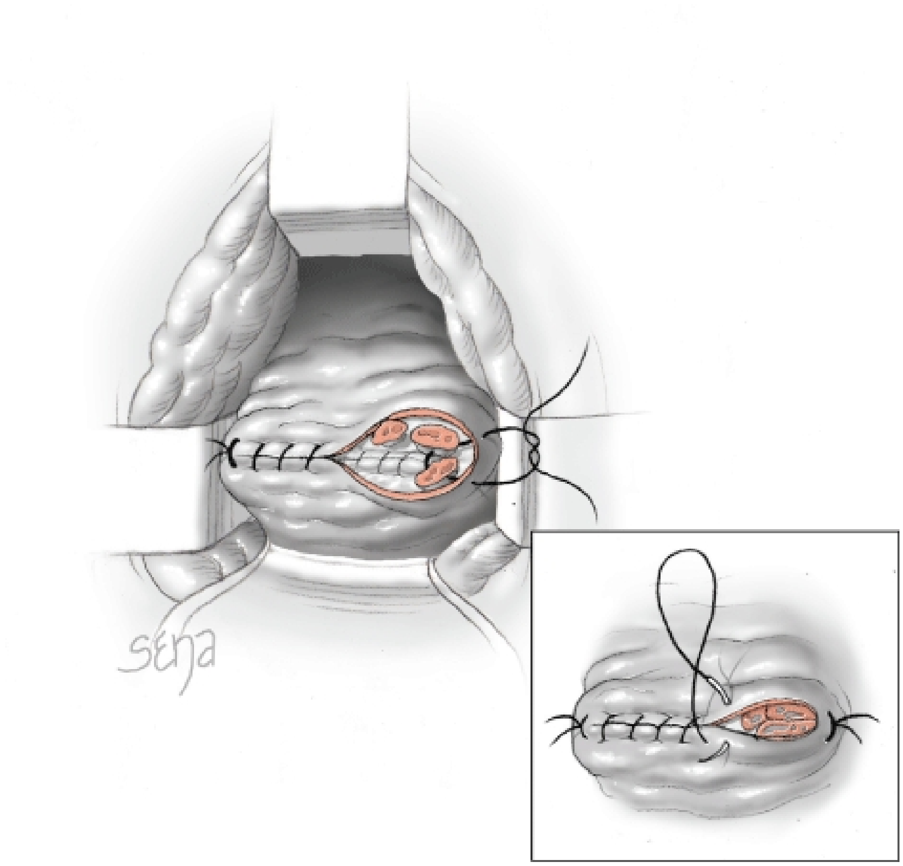
FIGURE 41-20.9



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Vaginal cuff closure.

FIGURE 41-20.10



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Vaginal cuff closure.

Postoperative

In general, patients following vaginal hysterectomy, compared with abdominal hysterectomy, typically have faster return of normal bowel function, easier ambulation, and decreased analgesia requirements. Evaluation and treatment of postoperative complications mirror those for abdominal hysterectomy.

41-21 LAPAROSCOPIC HYSTERECTOMY

Gynecology has fully embraced the laparoscopic approach to surgical procedures, and in the 1990s, a trend toward greater use of this modality for hysterectomy began. Several laparoscopic techniques have been developed for hysterectomy and vary depending on the degree of laparoscopic dissection versus vaginal surgery required to remove the uterus (Garry, 1994). These include

- Diagnostic laparoscopy prior to vaginal hysterectomy (VH)
- Vaginal hysterectomy assisted by laparoscopy; that is, lysis of adhesions and/or excision of endometriosis prior to VH
- Laparoscopically assisted vaginal hysterectomy (LAVH): laparoscopic dissection down to, but not including, uterine artery transection
- Laparoscopic hysterectomy (LH): laparoscopic dissection, including uterine artery transection
- Total laparoscopic hysterectomy (TLH): complete laparoscopic excision of the uterus

Most hysterectomies performed currently in the United States are either laparoscopically assisted vaginal hysterectomy (LAVH) or laparoscopic hysterectomy (LH).

Intraoperative

INSTRUMENTS

A number of instruments have been developed to assist the laparoscopic surgeon and to provide functions similar to those afforded by laparotomic tools. Vessel occlusion is an important component of any hysterectomy. For this, several different instruments have been used and include monopolar or bipolar grasping forceps, harmonic scalpel, stapling devices, and extracorporeal suturing. Of these modalities, the harmonic scalpel has gained increasing popularity because of its ability to cut cleanly with minimal smoke plume and little surrounding thermal tissue damage (see Chap. 40, Ultrasonic Scalpel).

Surgical Steps

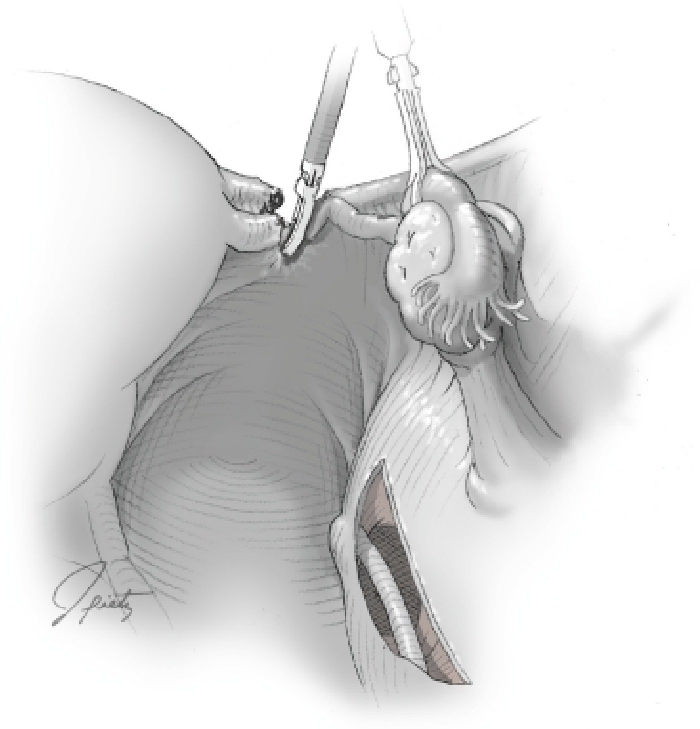
1. **Anesthesia and Patient Positioning.** For most women, these procedures are performed as an inpatient procedure under general or regional anesthesia. The patient is placed in a low dorsal lithotomy position, the vagina is surgically prepped, and a Foley catheter is placed.

2. **Initial Steps.** The introductory steps for LH mirror that for other laparoscopic procedures (see Laparoscopy). The number of trocars and their caliber may vary, but in general, LH requires a 10- to 12-mm trocar placed below the umbilicus and two or three secondary access trocars placed through the lower abdominal wall. Two trocars are placed beyond the lateral borders of the rectus abdominis muscle, whereas a third may be positioned centrally and cephalad to the uterine fundus.

   The patient is placed in Trendelenburg position to aid displacement of the bowel from the operating field. A blunt probe also is often helpful with bowel displacement. The pelvis and abdomen are inspected, and adhesions are lysed to restore normal anatomy.

3. **Ureter Identification.** Irrigating fluids and CO_2 used for insufflation can with time create edema of the peritoneum and hinder visualization of structures beneath it. For this reason, the ureters should be identified early. In many cases, the ureters can be visualized without difficulty beneath the pelvic peritoneum. However, it is sometimes necessary to open the peritoneum for identification. In such situations, the peritoneum medial to the infundibulopelvic (IP) ligament and overlying the ureter is grasped and tented using atraumatic forceps and incised with scissors. An irrigating probe is used to force water beneath and elevate the peritoneum for easier incision. The opening in the peritoneum then is extended caudally and cephalad along the length of the ureter. Through this peritoneal window, the ureter is identified (Fig. 41-21.1) (Parker, 2004).

FIGURE 41-21.1



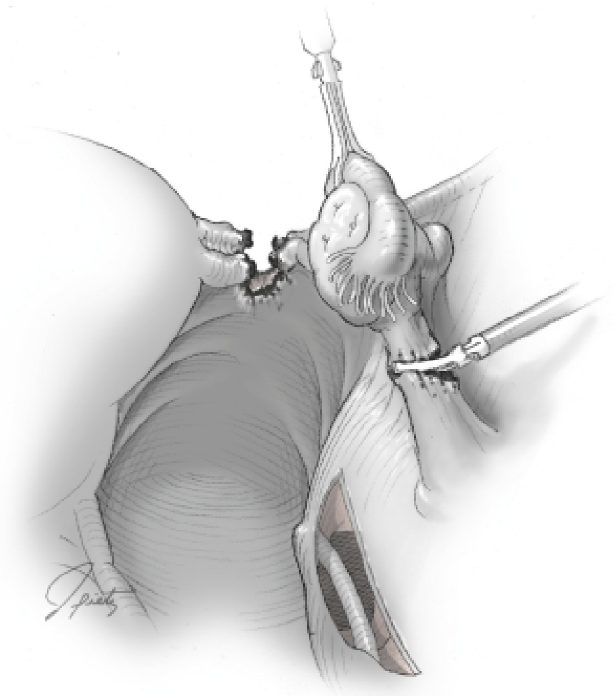
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Ureter identification. Fallopian tube and round ligament transection.

4. **Ovarian Conservation.** If preservation of the ovaries is planned, proximal portions of the round ligament, fallopian tube, and utero-ovarian ligament are desiccated and transected (Fig. 41-21.1).

5. **Oophorectomy.** If removal of the ovaries is desired, the infundibulopelvic (IP) ligament is grasped and pulled up and away from retroperitoneal structures. It is desiccated or stapled, and then divided (Fig. 41-21.2). The proximal portions of the round ligament, fallopian tube, and utero-ovarian ligament are desiccated and transected. The broad ligament beneath the adnexa is then sharply incised to free the adnexa.

FIGURE 41-21.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Infundibulopelvic ligament transection.

6. **Broad Ligament Incision.** With hysterectomy, incisions in the right and left anterior leaves of the broad ligament are directed caudally and centrally to meet in the midline above the vesicouterine fold. The posterior leaf requires incision caudally to the level of the uterosacral ligament. The loose areolar tissue separating the anterior and posterior leaves is dissected as well.

7. **Bladder Flap Development.** The vesicouterine edge is grasped with atraumatic forceps and elevated. This exposes connective tissue between the bladder and underlying uterus. This tissue then is dissected. Of the hysterectomy types, LH has the highest risk of bladder injury, and injury occurs most frequently to the dome during this sharp or blunt dissection (Harkki, 2001).

8. **Uterine Artery Transection.** After the uterine arteries are identified, the areolar connective tissue surrounding them is grasped, placed on tension, and incised. This skeletonizing of the vessels leads to superior occlusion of the uterine artery and vein. The arteries then are dessicated and transected. Alternatively, surgeons may elect to terminate the laparoscopic portion prior to uterine artery transection and complete artery ligation from a vaginal approach (LAVH).

   The ureters are also at greater risk during LH compared with other hysterectomy approaches (Harkki-Siren, 1998). Kuno and colleagues (1998) evaluated the use of ureteral catheterization to prevent such injury but found no benefit.

9. **Vaginal Hysterectomy.** With LH, after the uterine arteries are transected, the surgical approach is converted to that for

vaginal hysterectomy and completed as outlined in Section 41-20, Vaginal Hysterectomy. In this transition, the patient is repositioned from low dorsal lithotomy to standard or high lithotomy positions.

10. **Abdominal Inspection.** After vaginal completion of the hysterectomy, attention is redirected to laparoscopic inspection of the pelvis for signs of bleeding. The pelvis is irrigated and suctioned free of blood. The laparoscopic procedure is terminated as outlined in Laparoscopy.

Postoperative

Following LH, patient recovery mirrors that for vaginal hysterectomy.

41-22 LAPAROSCOPIC SUPRACERVICAL HYSTERECTOMY

Laparoscopic supracervial hysterectomy (LSH) differs from total laparoscopic hysterectomy (TLH) in that the uterine corpus is amputated, but the cervix remains. Once freed, the corpus is either delivered through a colpotomy incision or more commonly, is morcellated and removed through laparoscopic incisions. Different names for the procedure reflect minor variations in technique and include

- CISHâ€”cervical intrafacial Semm hysterectomy
- CASHâ€”classic abdominal Semm hysterecomy
- LASHâ€”laparoscopic supracervical hysterectomy
- SPLASHâ€”single-puncture laparoscopic supracervical hysterectomy.

The LASH technique is described below.

Intraoperative

INSTRUMENTS

During cervical amputation, blunt scissors, harmonic scalpel, morcellator knife, laser, or monopolar scissors may be used to excise the corpus. Of these modalities, the harmonic scalpel is favored because it offers the cleanest separation lines, smallest cautery plume, and least thermal damage to surrounding tissues.

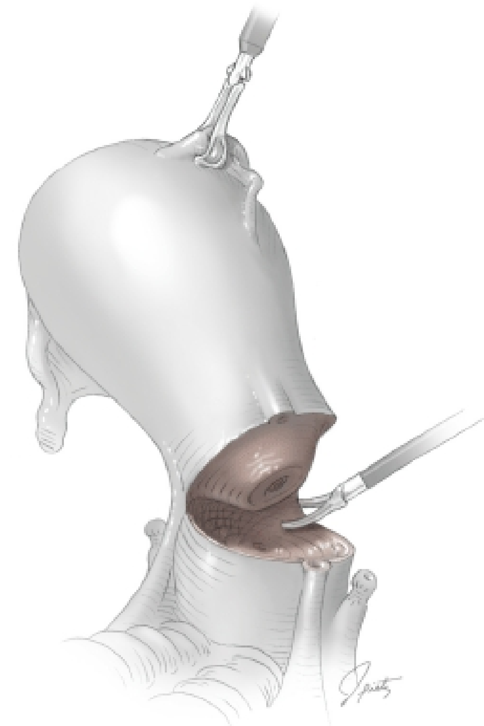
Once the corpus has been freed, it must be removed from the abdomen. Previously, colpotomy was used, but with the development of electric morcellating devices, vaginal removal of the specimen is no longer required. With most devices, tissue is grasped and drawn into a sheath that contains a rotating surgical blade to cut tissues. Because of the potential for surrounding organ injury, morcellators should not be moved toward the tissue of interest, but rather those tissues are brought to it (Milad, 2003).

Surgical Steps

1. **Initial Steps.** The initial surgical steps for LSH mirror those for LH, including coagulation of the uterine vessels (see Section 41-21, Laparoscopic Hysterectomy).

2. **Uterine Amputation.** The corpus is amputated from the cervix at a point just below the internal cervical os and superior to the uterosacral ligaments. A conical incision is extended down into the cervix to limit the possibility of residual endometrium (Fig. 41-22.1) (Jenkins, 2004). Additionally, at this point, adjunctive coring or ablation of the endocervical canal also may be performed to decrease the risk of long-term postoperative bleeding.

FIGURE 41-22.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Uterine amputation.

3. **Hemostasis.** Points of bleeding are cauterized, and the surgeon may elect to suture the peritoneum to cover the cervical stump. Alternatively, the use of absorbable adhesion barriers (Interceed, Johnson and Johnson, New Brunswick, NJ) at the surgical site is increasing in popularity.

4. **Laparoscopy Final Steps.** Completion of the procedure follows that for general laparoscopic procedures (see Laparoscopy).

Postoperative

Advantages to laparoscopy include a rapid return to normal diet and activities. Sexual intercourse, however, is delayed for several weeks following surgery to allow adequate healing.

41-23 TRACHELECTOMY

During the 1920s through 1950s, most abdominal hysterectomies were supracervical due to the lack of adequate blood banking and antibiotic therapy. For many women who had supracervical hysterectomy, later surgical removal of the cervix, which is termed *trachelectomy,* often was indicated for complaints of vault prolapse, persistent cyclic bleeding, or preinvasive cervical lesions (Pasley, 1988).

The cervix may be removed either vaginally or abdominally. However, for most women without concurrent pelvic pathology, vaginal trachelectomy is preferred (Pratt, 1976). With the resurgence of supracervical hysterectomy, now performed via laparoscopy, rates of trachelectomy for benign causes are expected to rise in the future.

Preoperative

PATIENT EVALUATION

As with hysterectomy, to exclude invasive cervical cancer, women preoperatively require Pap smear screening.

CONSENT

Trachelectomy is a safe and effective procedure. However, as with vaginal hysterectomy, patients are at risk for urinary tract and bowel injury. Similarly, postoperative vaginal cuff complications may include hematoma, abscess, and cellulitis. Fortunately, complications are infrequent for most. Although Pratt and Jeffries (1976) noted complications in 91 of 262 patients, complication rates in several series ranges below 10 percent (Welch, 1959; Riva, 1961).

PATIENT PREPARATION

Entry into the peritoneal cavity is common during trachelectomy. Accordingly, as with vaginal hysterectomy, antibiotic prophylaxis is warranted. Enemas the evening prior to surgery aid in evacuation of the rectum and minimize fecal soiling of the operative field.

Intraoperative

Surgical Steps

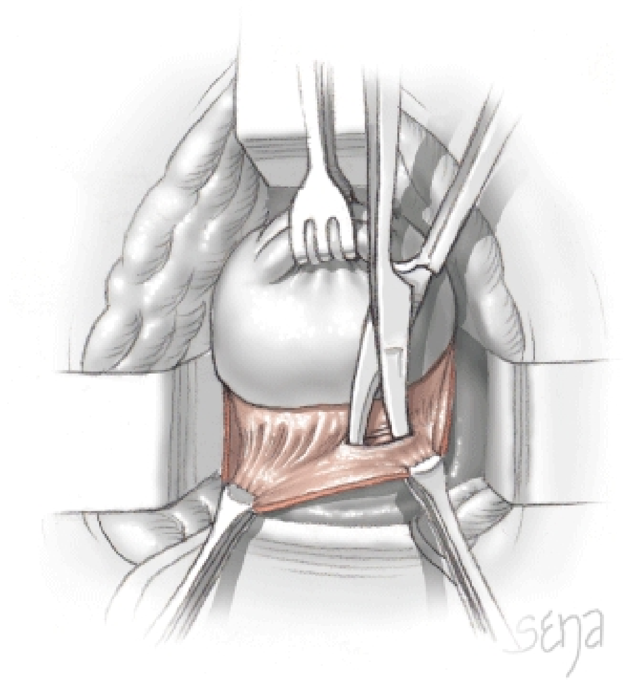
1. **Anesthesia and Patient Positioning.** For most women, trachelectomy is performed as an inpatient procedure under general or regional anesthesia. The patient is placed in a high or a standard dorsal lithotomy position, the vagina is surgically prepped, and a Foley catheter is placed.

2. **Vaginal Wall Incision.** The beginning steps of trachelectomy mirror those for vaginal hysterectomy (see Section 41-20, Vaginal Hysterectomy, steps 2 & 3).

3. **Extraperitoneal Dissection.** However, unlike vaginal hysterectomy, because the cervical stump lies outside the peritoneum, entry into the peritoneal cavity is not required for trachelectomy. Accordingly, following circumcision of the vaginal wall around the cervix, dissection proceeds to the vesicouterine fold but without peritoneal entry.

   In many cases, the bladder is more densely adhered to the anterior cervix. Thus, the clear tissue planes often encountered during vaginal hysterectomy are absent. Moreover, if at completion of the original hysterectomy the peritoneum was re-approximated to cover the cervical stump, then the bladder may be draped over and scarred to the apex of the stump as well. For this reason, dissection of the vaginal wall, bladder, and rectum from the surface of the cervix typically requires sharp rather than blunt dissection (Fig. 41-23.1). As with vaginal hysterectomy, outward traction on the cervix in combination with countertraction of the vaginal wall aids dissection. To avoid cystotomy and proctotomy, scissor blades and dissecting pressure are directed against the cervix.

FIGURE 41-23.1

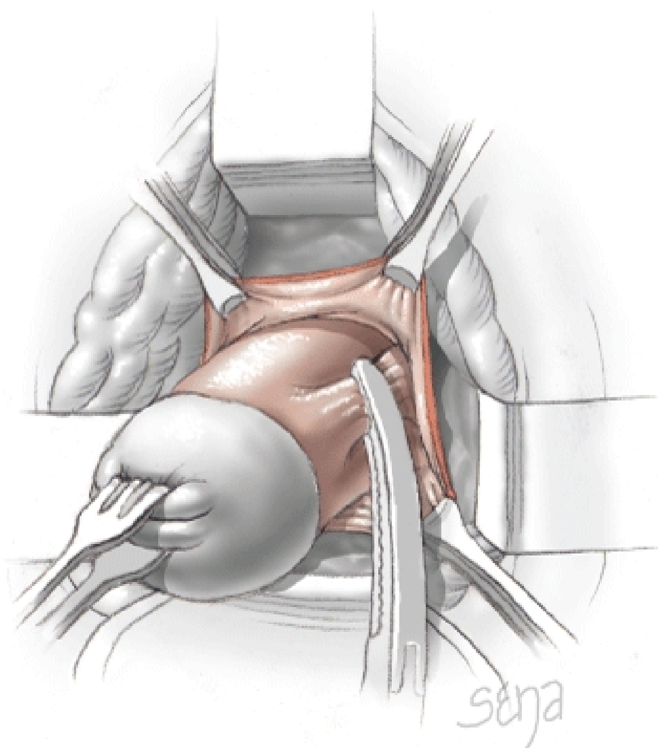


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Extraperitoneal dissection.

4. **Transection of Uterosacral and Cardinal Ligaments.** Once dissected free from the vaginal wall, the uterosacral and cardinal ligaments are clamped and ligated as with vaginal hysterectomy (Fig. 41-23.2). The cervical branches of the uterine artery typically are clamped and ligated within the cardinal ligament. Depending on cervical length, serial transection and ligation of the cardinal ligament are continued until the stump apex is reached.

FIGURE 41-23.2

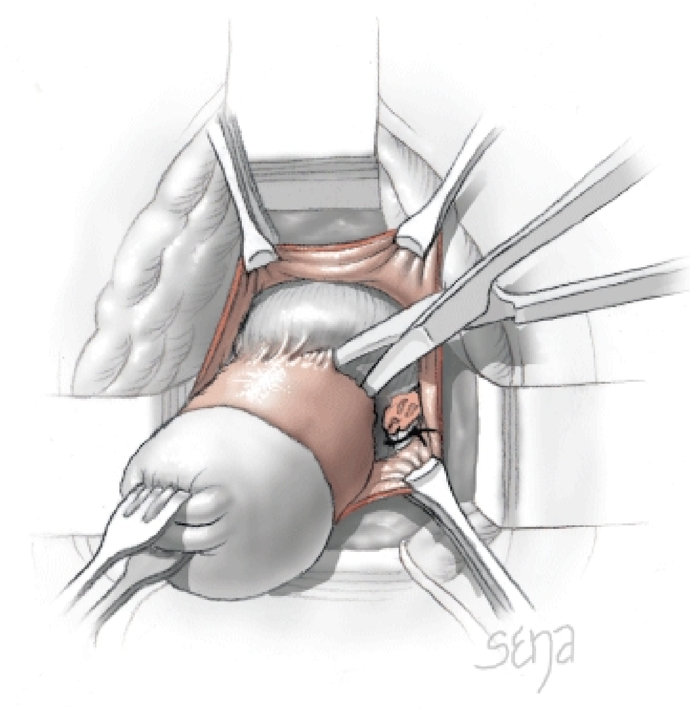


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Cardinal ligament.

5. **Stump Excision.** Once the apex is reached, sharp dissection across the top of the stump will free it from the vagina (Fig. 41-23.3).

FIGURE 41-23.3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Stump dissection from peritoneum.

6. **Incision Closure.** Incorporation of the uterosacral and cardinal ligaments and re-approximation of the vaginal walls follow those for vaginal hysterectomy (Figs. 41-20.9 and 41-20.10).

Postoperative

As with hysterectomy, a significant number of women will have unexplained fever following trachelectomy. Pasley (1988), in his series of 55 patients, noted a rate of 9 percent. Similar to hysterectomy, patients with persistent or high-degree fevers require evaluation and antibiotic treatment.

41-24 INTERVAL PARTIAL SALPINGECTOMY

Interval partial salpingectomy is similar to puerperal midsegment salpingectomy and differs mainly in procedure timing and the method of abdominal entry. In contrast to postpartum or postabortal sterilization, the term *interval* designates performance unrelated in time to pregnancy. Accordingly, for most women undergoing interval sterilization, the uterus is small and lies within the confines of the pelvis. Thus, fallopian tubes are reached either laparoscopically or through a low transverse incision.

In general, with interval partial salpingectomy, a midtubal segment of fallopian tube is excised, and the severed ends seal by fibrosis and reperitonealization. Commonly used methods of interval sterilization include the Parkland, Pomeroy, and modified Pomeroy techniques (American College of Obstetricians and Gynecologists, 2003). Rarely, Irving and Uchida techniques are used.

With these latter two methods, increased dissection, operative time, and chance of mesosalpingeal injury are significant disadvantages.

Of methods for tubal sterilization, interval partial salpingectomy via laparotomy is selected infrequently, and only about 4 percent of women in the United States who elect sterilization undergo this procedure (Peterson, 1996). More commonly, laparoscopic techniques are employed mainly because of the postoperative advantages linked with laparoscopy (see Laparoscopy). Accordingly, interval partial salpingectomy typically is selected for cases in which laparoscopy may not be indicated, such as women with extensive adhesions, those with other concurrent pelvic pathology that dictates laparotomy, or situations in which laparoscopic equipment or surgical skills are lacking.

Preoperative

CONSENT

Prior to surgery, women can be reassured that partial salpingectomy is an effective method of sterilization. Pregnancy rates well less than 1 percent are typical. This result from tubal recanalization or technical errors, such as ligation of the wrong structure.

Tubal sterilization is a safe surgical procedure, and complication rates range below 2 percent (Pati, 2000). Of these, anesthesia complications, organ injury, and infection are the most frequent. In addition, although pregnancy is uncommon following sterilization, when pregnancy does occur, the risk of ectopic pregnancy is high and approximates 30 percent (Peterson, 1996; Ryder, 1999). However, because tubal sterilization is highly effective contraception, the overall risk of pregnancy is low, and therefore, so also is the risk of ectopic pregnancy.

Aside from physical risks, a small percentage of women experience regret following sterilization (see Chap. 5, Cautions). In studies, rates of regret approach 15 percent (Hillis, 1999; Trussell, 2003). For this reason, prior to surgery, women should be counseled about the risk of regret, the permanence of the procedure, and alternative effective long-term contraceptive methods.

Intraoperative

Surgical Steps

1. **Anesthesia and Patient Positioning.** Interval partial salpingectomy typically is an outpatient procedure performed under general anesthesia or regional analgesia. Following administration of anesthesia, the patient is placed supine, the abdomen surgically prepped, and the bladder is drained.

2. **Minilaparotomy.** For most patients, a 3- to 5-cm minilaparotomy incision cut at the level of the uterine fundus is sufficient and should follow the steps outlined in Section 41-2, Pfannenstiel Incision. Small Richardson or Army-Navy retractors provide adequate visualization in most cases. A uterine manipulator may be helpful in bringing the fallopian tubes into view.

3. **Tubal Identification.** A common reason for sterilization failure is ligation of the wrong structure, typically the round ligament. Identification and isolation of the fallopian tube prior to ligation and submission of tubal segments for pathologic confirmation therefore are required. In some women, especially those with associated tubal adhesions, this step may be challenging.

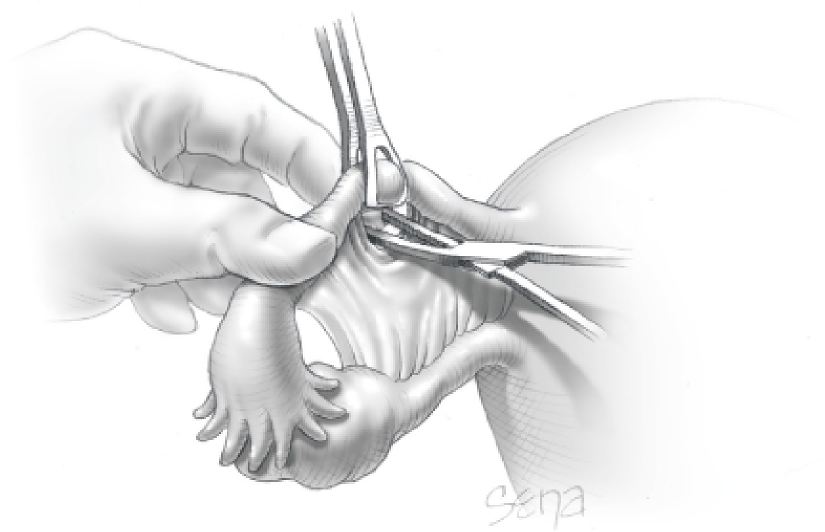
   Initially, the uterine fundus is identified. At the cornua, insertion of the fallopian tube lies posterior to that of the round ligament, and this orientation can guide a surgeon initially to the correct structure. A primary Babcock clamp is used to elevate the fallopian tube proximally, whereas a second grasps the tube more distally. The first clamp then is moved again and is placed distal to the second. The second then is removed and again placed distal to the first. In this manner, the surgeon "marches" down the length of the tube to reach the ampulla and identify the fimbria.

4. **Tubal Ligation.** At the midpoint of the tube, an avascular space in the mesosalpinx is identified, and a hemostat is placed directly beneath the tube. The hemostat is advanced bluntly through the mesosalpinx as counterpressure is applied with the index finger. The selected site should allow excision of a 2-cm segment that does not incorporate the fimbrial portion of the tube. Ligation of this portion leads to a greater risk of tubal recanalization and higher failure rates.

   The hemostat is advanced through the defect and gently opened to expand the aperture (Fig. 41-24.1). The end of a 2-0

chromic free tie is placed in the tip of the hemostat and pulled through the opening. This is repeated, bringing another tie through the rent. The distal portion of the midsegment is lifted, and the distal suture is tied. This elevation allows for a larger tubal segment to be obtained and helps the cut ends to remain widely separated. The second tie then is secured around the proximal fallopian tube.

FIGURE 41-24.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Parkland method: opening created in mesosalpinx.

5. **Tubal Excision.** The tip of Metzenbaum scissors is inserted through the mesosalpingeal defect, and the proximal portion of the tube is cut. A 0.5-cm pedicle is left to ensure that the tube will not slip through its ligature (Fig. 41-24.2). The inferior aspect of the tube is dissected sharply from the mesosalpinx toward the distal ligature, freeing the tube from the mesosalpinx. The distal end is excised above the suture, and an adequate 2-cm segment of tube is obtained. The pedicles and mesosalpinx are inspected for hemostasis. The procedure then is repeated on the other side.

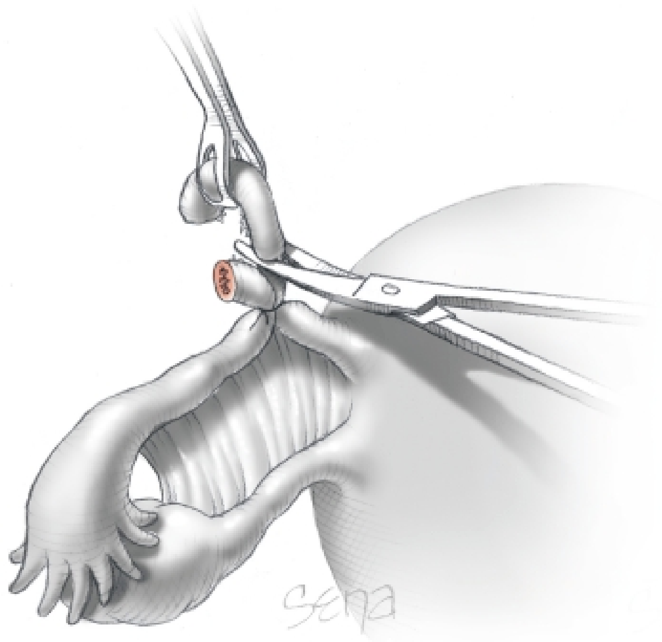
FIGURE 41-24.2

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Parkland method: tubal excision.

6. **Pomeroy Method.** This technique involves grasping and elevating a 2-cm midsegment of tube, ligating the tubal loop with a 2-0 chromic or plain catgut suture, and then excising the distal portion of the loop (Fig. 41-24.3). Prompt absorption of the suture following surgery causes the ligated ends to fall away, with a resulting 2- to 3-cm gap.

FIGURE 41-24.3

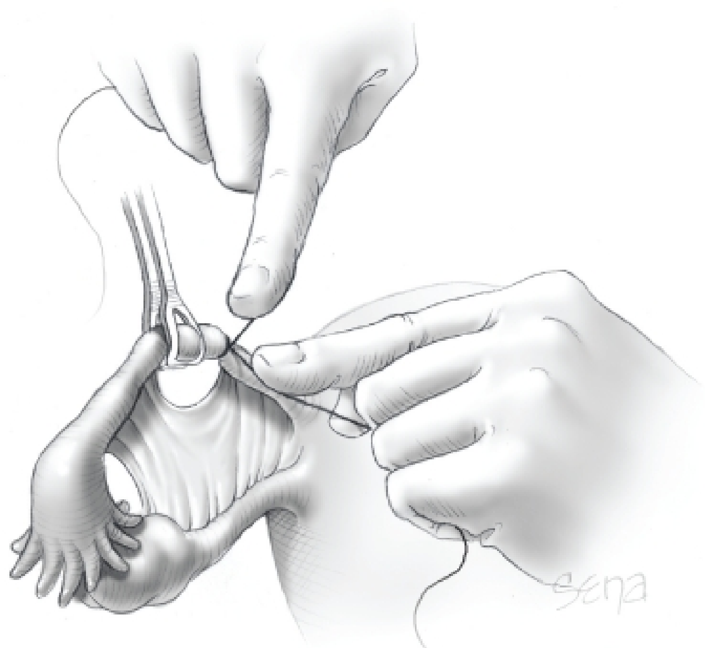


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Pomeroy method.

7. **Modified Pomeroy Method.** Many modifications of the Pomeroy technique have been described. One technique creates an avascular window in the mesosalpinx at a midpoint along the tube. Through this window, suture similar to that used for the Pomeroy method is passed. The portion of tube that lies proximal to this window is ligated first (Fig. 41-24.4). The long ends of this suture then are tied around the entire tubal loop, as in the Pomeroy method (Fig. 41-24.3). The distal portion of the loop is excised.

FIGURE 41-24.4

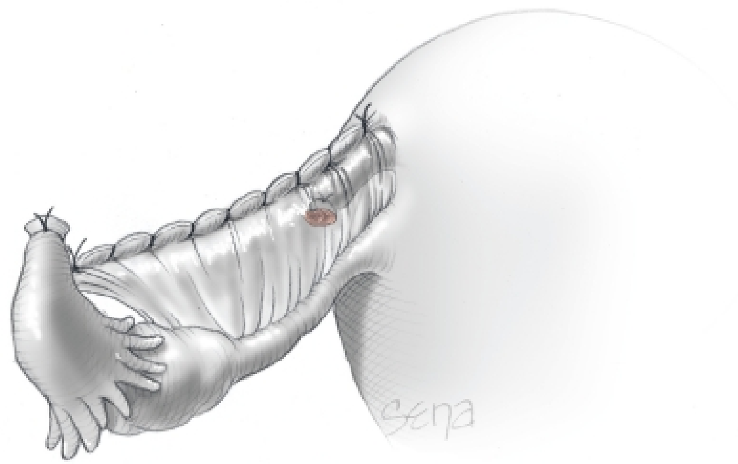


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Modified Pomeroy method.

8. **Uchida Method.** Tubal serosa is first separated from the muscularis by a subserosal injection of a dilute saline solution of epinephrine (1:100,000). A longitudinal incision is made in the ballooned serosa on its surface opposite the mesosalpinx. The serosal peritoneum then is grasped and dissected away from the underlying tubal muscularis. Following this dissection, a 5-cm midsegment of dissected fallopian tube is ligated proximally and distally with 2-0 chromic or plain catgut suture, and then resected. The raw serosal edges are reapproximated, burying the proximal cut tubal end within the leaves of the broad ligament and exteriorizing the distal end from the broad ligament (Fig. 41-24.5) (Sklar, 2004).

FIGURE 41-24.5

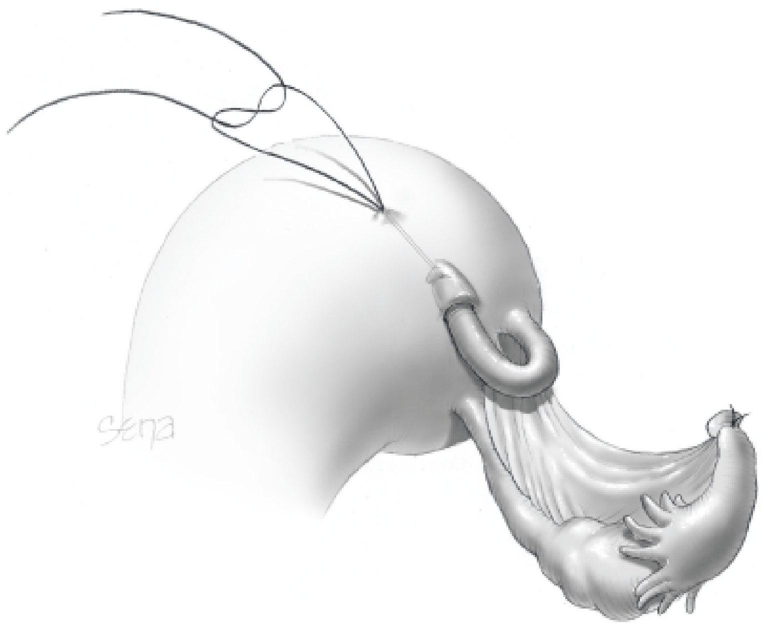


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Uchida method.

9. **Irving Method.** The Irving method begins similarly to the Parkland method. However, after the knot on the proximal tubal segment is secured, the ties are left long. Near the cornua, a 1-cm incision is made into the uterine serosa on the posterior uterine wall (Fig. 41-24.6). From this incision, a hemostat is used to tunnel into the myometrium, creating a 1- to 2-cm pocket that lies deep but parallel to the serosa. The two free ends of the proximal stump ligature then are threaded onto a curved needle. The needle is driven deep into the myometrial tunnel and exits out onto the uterine serosa. The needle is removed, and traction on the sutures pulls the proximal tubal stump into the pocket. Sutures then are tied on the outside of the serosa. The opening of the tunnel then is closed around the tube with interrupted 2-0 absorbable sutures.

FIGURE 41-24.6



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Irving method.

10. **Wound Closure.** The wound is closed as for other transverse abdominal incisions (see Section 41-2, Pfannenstiel Incision).

Postoperative

The recovery following minilaparotomy typically is rapid and without complication, and women may resume their regular diet and activities as tolerated. Sterilization is immediate following surgery, and intercourse may resume at the patient's discretion. Aside from regret, the risk of long-term physical or psychologicol sequelae is low. Peterson and co-workers (2000) found that women who had undergone tubal sterilization were no more likely than those without this surgery to have menstrual abnormalities. Moreover, interval tubal ligation is unlikely to result in changed sexual interest or pleasure (Costello, 2002).

41-25 SALPINGECTOMY AND SALPINGOSTOMY

Salpingectomy involves removal of the fallopian tube with sparing of the ovary. Its predominant use is in the treatment of ectopic pregnancy. This surgery, however, also may be employed to remove hydrosalpinges to improve in vitro fertilization (IVF) success rates or may be used as a method of sterilization (see Chap. 9, Hydrosalpinx). Alternatively, *salpingostomy* describes a lengthwise linear incision of the fallopian tube and typically is used to remove ectopic pregnancy contents (see Chap. 7, Salpingostomy).

Laparoscopic surgery offers patients the advantages of shorter hospitalizations, quicker recoveries, and less postoperative pain (Murphy, 1992; Vermesh, 1989). For these reasons, laparoscopic treatment of ectopic pregnancy generally is preferred.

As a result, laparotomic approaches for salpingectomy and salpingostomy are now reserved only for patients with ruptured ectopic pregnancies who are hemodynamically unstable or in those who have contraindications to laparoscopy. In these instances, laparotomy offers faster entry into the abdomen for control of bleeding and greater patient safety.

Preoperative

CONSENT

Most complications associated with salpingectomy and salpingostomy occur in conjunction with ectopic pregnancies, and the risk of bleeding is prominent. Injury to the ipsilateral ovary, however, is an attendant risk regardless of the indication. In certain cases, if severe, this damage can demand concurrent oophorectomy.

Persistent Trophoblastic Tissue

Following any surgical treatment of ectopic pregnancy, trophoblastic tissue can persist. Remnant implants typically involve the fallopian tube, but extratubal trophoblastic implants have been found on the omentum and on pelvic and abdominal peritoneal surfaces. Peritoneal implants typically measure 0.3 to 2.0 cm and appear as red-black nodules (Doss, 1998).

The risk of persistent trophoblast tissue is lower with salpingectomy than with salpingostomy. In addition, the risk is lowest with laparotomic salpingectomy because morcellation of the tube during laparoscopic salpingectomy also can leave trophoblastic tissue behind (Farquhar, 2005).

Preservation of Fertility

Most, but not all, studies show comparable subsequent fertility rates whether salpingectomy or salpingostomy is performed (Bangsgaard, 2003; Clausen, 1996; Mol, 1998; Tulandi, 1999). A further discussion of fertility and the long-term outcomes from these procedures can be found in Chapter 7, Salpingostomy. In the presence of a healthy contralateral tube, therefore, neither salpingostomy nor salpingectomy offers an advantage with respect to future fertility. However, salpingostomy should be considered as the primary treatment option for tubal pregnancy in the presence of disease in the contralateral tube and a desire for future fertility.

Unfortunately, in some cases of rupture, the extent of tubal damage or bleeding may limit tubal salvage, and salpingectomy may be required.

PATIENT PREPARATION

Salpingectomy and salpingostomy are associated with low rates of infection. Accordingly, preoperative antibiotics usually are not required.

Intraoperative

Surgical Steps

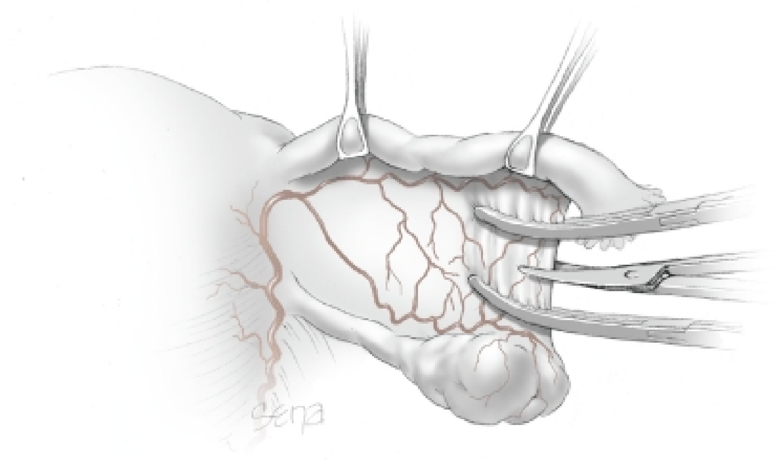
1. **Anesthesia and Patient Positioning.** In most cases of ectopic pregnancy managed by laparotomy, surgery is an inpatient procedure and requires general anesthesia. The patient is positioned supine, a Foley catheter is placed, and bladder is drained.

2. **Abdominal Entry.** The overwhelming majority of laparotomic salpingectomy procedures can be managed using a Pfannenstiel incision (see Section 41-2, Pfannenstiel Incision).

3. **Salpingectomy.** Once access to the pelvic organs has been reached, the adnexa are elevated and evaluated. For the affected fallopian tube, a Babock clamp is placed around the tube and directs the tube away from the uterus and ovary. This extends the mesosalpinx (Fig. 41-25.1).

   Beginning at the distal, fimbriated end of the tube, one Kelly clamp is placed across a 2-cm-long segment of the mesosalpinx, close to the fallopian tube. Another clamp is placed similarly but lies closer to the ovary. These clamps occlude vessels that traverse the mesosalpinx. Scissors then cut the interposed mesosalpinx.

FIGURE 41-25.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

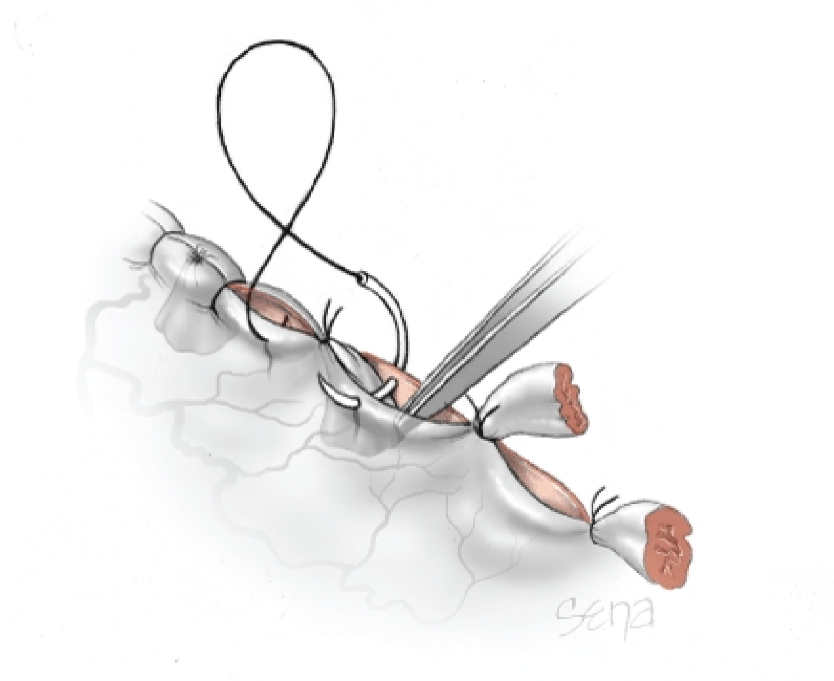
Salpingectomy.

4. **Vessel Ligation.** Each vascular tissue pedicle close to the ovary is tied with 2-0 or 3-0 delayed-absorbable suture. The clamp close to the tube may remain and is eventually removed with the tube. This step is repeated serially and with each clamping, an approximately 2-cm length of mesosalpinx is incorporated. Progression is directed from the ampullary end of the tube toward the uterus.

   The last clamp is placed across the proximal mesosalpinx and fallopian tube. Scissors then cut the mesosalpinx and free the tube from the uterus. This pedicle is similarly ligated with suture.

5. **Wound Closure.** If the surgeon so desires, the exposed vascular pedicles may be covered by a running suture that approximates the mesosalpinx (Fig. 41-25.2). The pelvis is irrigated and rid of blood and tissue dÃ©bris. The abdominal incision is closed as described in Section 41-2, Pfannenstiel Incision.

FIGURE 41-25.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Mesosalpinx closure.

6. **Salpingostomy.** Surgical steps for salpingostomy mirror those used in laparoscopic salpingostomy and can be reviewed in Section 41-31, Laparoscopic Salpingostomy.

Postoperative

In cases performed for ectopic pregnancy, salpingectomy or salpingostomy represents pregnancy termination. For this reason, the Rh status of the patient should be evaluated. Administration of 50 or 300 μg (1,500 IU) Rh_0 [D] immune globulin intramuscularly within 72 hours of pregnancy termination in Rh-negative women can lower the risk of isoimmunization in future pregnancies dramatically.

Because of the increased risk of persistent trophoblastic tissue in patients undergoing salpingostomy, serial weekly serum β-hCG levels should be measured until undetectable levels are reached. During this time, contraception should be used to avoid confusion between persistent trophoblastic tissue and a new pregnancy.

Resumption of activity and diet may follow that of a Pfannenstiel incision, as discussed in Section 41-2, Pfannenstiel Incision.

41-26 OVARIAN CYSTECTOMY

The removal of ovarian cysts usually is prompted by patient symptoms or by concerns of ovarian malignancy. Rather than excision of the entire ovary, removal of the cyst alone can offer women with ovarian pathology an opportunity to preserve hormone function and reproductive capacity (Maneschi, 1993). For these reasons, goals of ovarian cystectomy include gentle handling of tissues to limit postoperative adhesion formation and reconstruction of normal ovarian anatomy to aid the transfer of ova to the fallopian tube.

In some patients, a cystectomy may be performed laparoscopically rather than through laparotomy (see Section 41-33, Laparoscopic Ovarian Cystectomy). Several studies support the safe and effective use of laparoscopy for this problem (Lin, 1995; Mais, 1995; Pittaway, 1994; Yuen, 1997). Although laparoscopy is the preferred method of treatment, there are certain settings in which its role should be limited. In general, when a cyst is large, adhesive disease limits access and mobility, or the risk of malignancy is great, laparotomy instead should be performed. As summarized in Chapter 9, Surgical Excision, malignancy is suspected when cysts exceed 10 cm in diameter, concurrent ascites is present, preoperative serum tumor markers are elevated, and cyst contents appear complex or borders irregular on imaging.

Preoperative

CONSENT

In addition to the general surgical risks of laparotomy, the major risk of cystectomy is extensive bleeding from or injury to the ovary. These may necessitate removal of the entire ovary. If ovarian cancer is suspected prior to surgery, patients should be educated about the possibility surgical staging, including the need for hysterectomy and removal of both ovaries (see Chap. 35, Surgical Staging).

PATIENT PREPARATION

Antibiotics typically are not required preoperatively. If hysterectomy is required during ovarian staging, antibiotics may be given intraoperatively.

Intraoperative

Surgical Steps

1. **Anesthesia and Patient Positioning.** Because of the potential need for upper abdominal staging if malignancy is found, general anesthesia typically is indicated for this inpatient procedure. The patient is placed in a supine position, the abdomen and vagina are surgically prepped, and a Foley catheter is placed. Because of a possible need for hysterectomy if malignancy is found, the vagina should be included in the process.

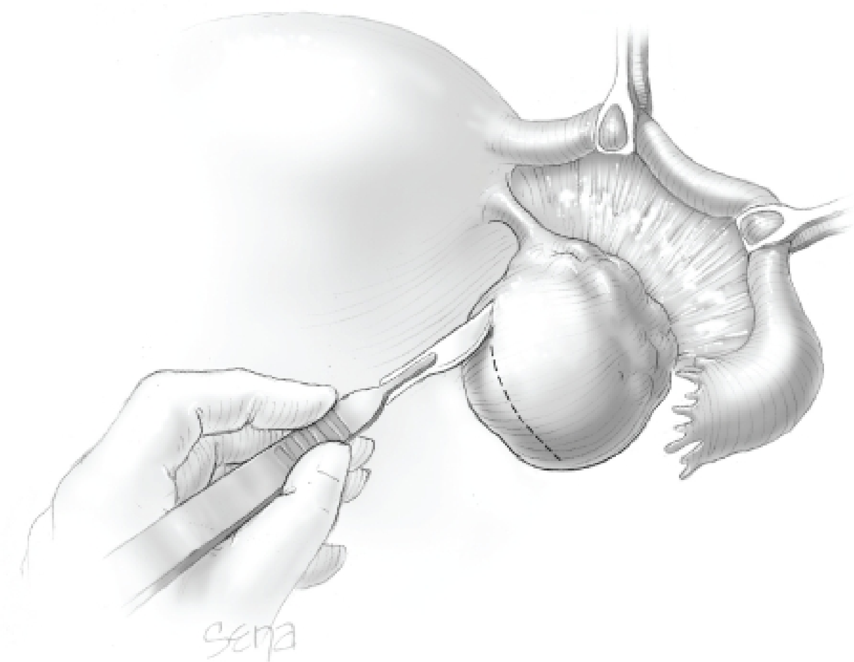
2. **Abdominal Entry.** Most ovarian cysts can be removed through a Pfannenstiel incision. Extremely large cysts or those in which a greater concern for malignancy is present may require a vertical incision. Vertical incisions allow adequate access to the upper abdomen if ovarian cancer staging is required.

   Cell washings from the pelvis and upper abdomen are collected. If a cancer is found, the washings are sent for cytologic analysis. If benign ovarian disease is found, then these washings may be discarded. The upper abdomen and pelvis are explored, and excrescences or suspicious areas are sampled and sent for frozen-section analysis.

   A self-retaining retractor is placed within the incision, and the bowel and omentum are packed from the operating field. The ovary is brought into view, and moist laparotomy sponges are placed in the cul-de-sac and beneath the ovary. This helps to minimize contamination of the pelvis if the cyst ruptures during excision.

3. **Ovarian Incision.** The ovary is held between the surgeon's thumb and opposing fingers. The ovarian capsule that overlies the dome of the cyst then is incised with either scalpel or electrosurgical blade. Care is taken to extend the incision deeply into the ovarian stroma to the level of the cyst wall but not to enter and rupture the cyst (Fig. 41-26.1). An intact cyst avoids spill of potentially malignant fluid into the peritoneal cavity. It also provides clearer planes of tissue dissection. Allis clamps are then placed on the incised edges of the ovarian capsule.

FIGURE 41-26.1

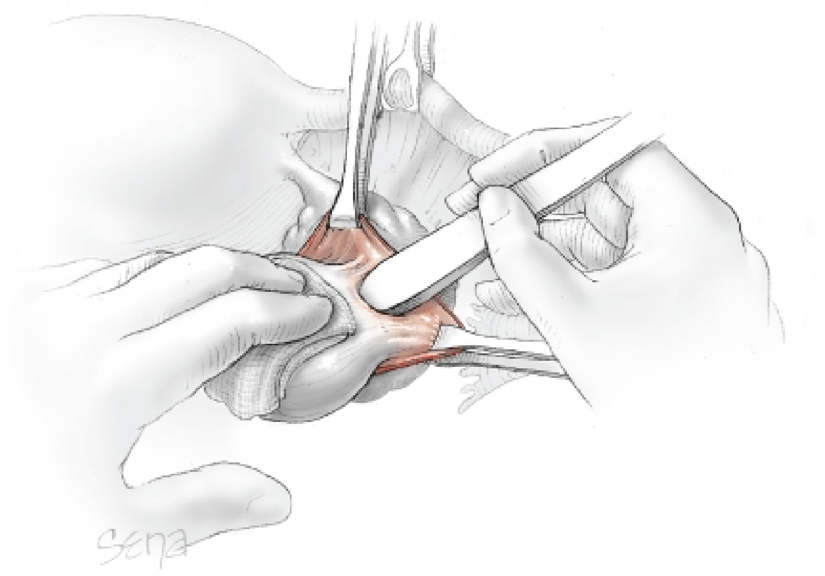


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Ovarian incision.

4. **Cyst Dissection.** Blunt dissection with fingertip or knife handle is used to develop a cleavage plane between the cyst wall and the remaining ovarian stroma (Fig. 41-26.2). In certain cases, adhesions may obliterate the cleavage plane, and sharp dissection with scissors may be necessary. As an assistant gently pulls the Allis clamps in a direction away from the cyst wall, the surgeon places fingers just above the advancing cleavage plane and pulls the cyst in the direction opposite the Allis clamps. Such traction and countertraction across the cleavage plane aids in dissection. Because the surface of the cyst wall may be smooth and slippery, the surgeon may place an unfolded thin gauze sponge between the fingers and the cyst wall to afford a better grip.

FIGURE 41-26.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

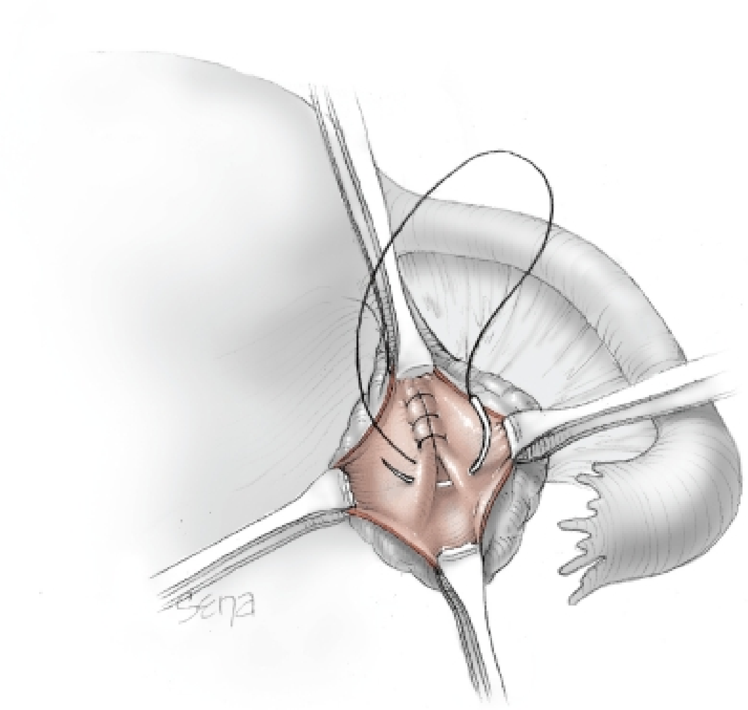
Cyst dissection.

5. **Cyst Excision.** Once the cyst is removed, it may be sent to the pathology department for frozen-section analysis. The ovarian bed is examined, and bleeding points are coagulated electrosurgically. In cases in which large cysts have stretched and thinned the ovarian surface, excess capsule can be removed sharply. This excision is performed to restore normal ovarian anatomy. Because ovarian follicles are contained within even extremely thinned capsules, however, care must be taken to preserve this tissue whenever possible.

6. **Ovarian Closure.** The ovarian bed then is closed in layers using 4-0 or 5-0 delayed-absorbable suture. These sutures re-approximate the ovarian tissue that previously surrounded the cyst on both sides (Fig. 41-26.3). In cases where the ovarian surface has been thinned, the needle tip should not be driven through the capsule. The resulting exposed suture on the ovarian surface may increase adhesion formation.

   The ovarian incision is closed with a running subcortical stitch (similar to subcuticular stitch) using 5-0 delayed-absorbable suture.

FIGURE 41-26.3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Ovarian closure.

7. **Incision Closure.** Laparotomy sponges are removed from the cul-de-sac, and the pelvis is copiously irrigated with an isotonic solution such as lactated Ringer solution. The remaining packs and retractor are removed, and the abdominal incision is closed as described in Section 41-1, Midline Vertical Incision or Section 41-2, Pfannenstiel Incision.

Postoperative

After surgery, care may follow that described for laparotomy in general (see Section 41-1, Midline Vertical Incision).

41-27 OOPHORECTOMY

Removal of an ovary is performed more commonly by laparoscopy. However, laparotomy typically is indicated if the potential for malignancy is great, if the ovary is larger than 8 to 10 cm, or if significant adhesions are anticipated. In many of these instances, a salpingo-oophorectomy is performed, as presented in Section 41-19, Hysterectomy. However, if future fertility is desired, then the fallopian tube is preserved whenever possible.

Preoperative

PATIENT EVALUATION

Oophorectomy typically is performed to remove ovarian pathology that has been identified using transvaginal or transabdominal sonography. In patients in whom anatomy may be unclear, magnetic resonance (MR) imaging may add additional information. As

described in Chapters 35, Imaging and 36, Diagnosis, tumor markers may be drawn prior to surgery if malignancy is suspected.

CONSENT

In general, serious complications with oophorectomy are low and similar to those with other intra-abdominal surgeries. These include organ injury, hemorrhage, wound infection, and anesthesia complications. In addition, the risk of injury to the adjacent fallopian tube or ureter is small but should be specifically discussed during the consenting process. Ovarian cysts are the most common indication for oophorectomy. In these cases, if a malignant cyst ruptures and spills its contents, patients should be aware of the possible negative effects on prognosis.

PATIENT PREPARATION

Unless an ovarian abscess is identified, antibiotic prophylaxis is administered according to the preference of the surgeon.

Intraoperative

Surgical Steps

1. **Anesthesia and Patient Positioning.** Oophorectomy performed via laparotomy typically requires general anesthesia to allow staging of the upper abdomen if malignancy is found. Following administration of anesthesia, the patient is positioned supine, a Foley catheter is placed, and the abdomen is surgically prepped.

2. **Abdominal Entry.** Either a transverse or a vertical incision may be used for oophorectomy (Sections 41-1, Midline Vertical Incision and 41-2, Pfannenstiel Incision). Clinical factors such as ovarian size and risk of malignancy influence this selection.

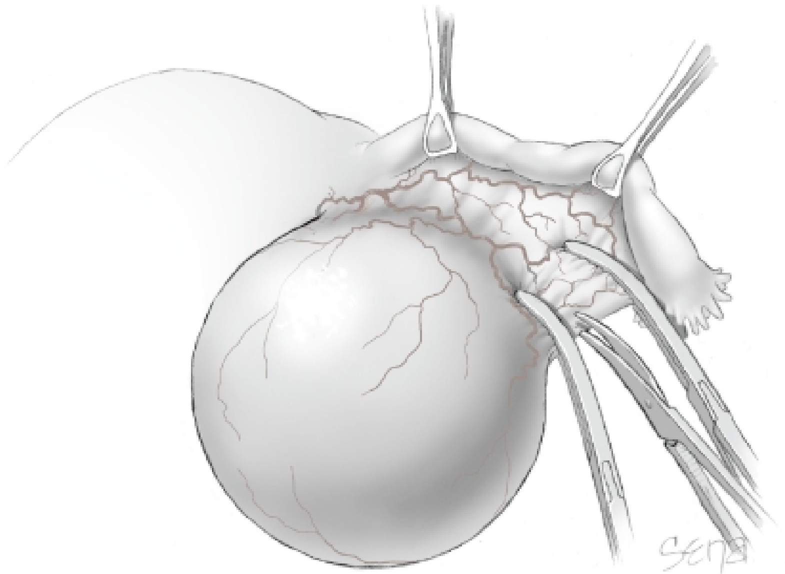
3. **Exposure.** Following entry into the abdomen, a self-retaining retractor such as an O'Connor-O'Sullivan or Balfour retractor is placed. The pelvis and abdomen are explored visually and manually, and the bowel is packed from the operating field. The affected adnexa is grasped and elevated from the pelvis. If extensive adhesions are present, normal anatomic relationships are restored.

4. **Ureter Location.** Because of the close proximity of the ureter to the infundibulopelvic ligament, the ureter is identified prior to clamps being placed.

5. **Meso-ovarium.** The ovary is lifted from the pelvis and inspected. If malignancy is suspected, pelvic washings are obtained and set aside until analysis of a frozen-section sample from the affected ovary is completed. Two Babcock clamps are place at points equidistant along the fallopian tube length and are extended and retracted away from the ovary by an assistant. The ovary is elevated and placed on gentle tension in the opposite direction from the tube (Fig. 41-27.1). This effectively fans out the meso-ovarium.

   The first Pean clamp is placed close to the ovarian wall and across the distal meso-ovarium. Depending on the size of the ovary, this tissue pedicle may be cut and ligated with 2-0 delayed-absorbable suture prior to placement of the next clamp. Alternatively, especially with large cysts, serial clamps may be placed across the meso-ovarium in a line toward the uterus (Fig. 41-27.2). Small bites are taken to avoid kinking of the fallopian tube. Once the most medial clamp is placed is placed across the ovarian ligament, curved Mayo scissors can be used to cut between the clamps. The freed ovary is removed from the operative site and sent to pathology for evaluation. If malignancy is suspected, a frozen section analysis is requested. All clamps on the meso-ovarium then are ligated (Fig. 41-27.2).

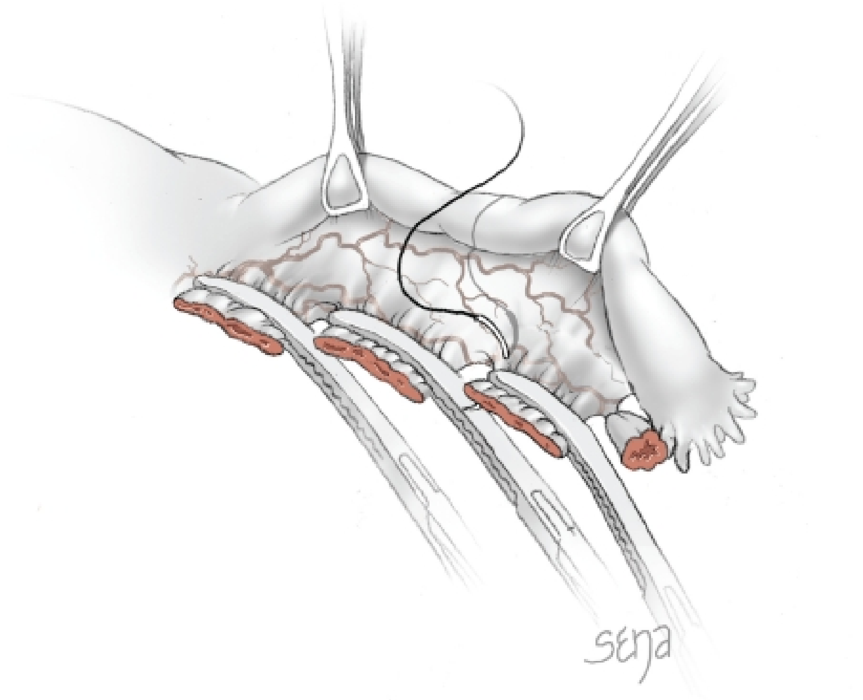
FIGURE 41-27.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Clamping the meso-ovarium.

FIGURE 41-27.2



Pedicle ligation.

6. **Wound Closure.** The retractor and packing sponges are removed from the abdomen. The abdominal incision then is closed as described in Section 41-1, Midline Vertical Incision or 41-2, Pfannenstiel Incision.

Postoperative

Patient recovery typically is without complication and is similar to that described for hysterectomy (see Section 41-19, Hysterectomy). In reproductive-aged women, if only one ovary is removed, hormone and reproductive function is preserved. However, if both are excised, then surgical menopause follows, and hormone replacement may be considered, as described in Chapter 22, Current Approach to Hormone Replacement Administration.

41-28 LAPAROSCOPY

Operative laparoscopy provides minimally invasive options for women undergoing gynecologic surgery. Initially used in diagnostic and sterilization procedures, the spectrum of laparoscopic surgeries now includes hysterectomy, myomectomy, pelvic lymph node dissection, and others.

As a group, studies evaluating complications associated with this procedure have attested to its safety, and complication rates typically are below 4 percent (Bateman, 1996; Fuller, 2003; Harkki-Siren, 1997b; Mirhashemi, 1998). Logically, a greater risk of complication has been associated with complex operative procedures compared with diagnostic or sterilization procedures (Hulka, 1995). Specifically, laparoscopic hysterectomy (LH) appears to be associated with the highest rates (Harkki-Siren, 1997b).

Preoperative

CONSENT

Laparoscopy typically is associated with few complications. Of these, organ injury caused by puncture or by electrosurgery tools is the most common major complication. If this occurs, or if surgery is hindered by bleeding or adhesions, conversion to laparotomy may be necessary. Overall, this conversion risk is low and approximates 5 percent.

In addition to organ damage, nerve or vascular injury also may result. Because patients are placed during some procedures for extended periods in the dorsal lithotomy position with arms abducted, injury to the common peroneal, femoral, and ulnar nerves and to the brachial plexus is possible (Philosophe, 2003; Schwartz, 1993). Rarely, air embolism from gas insufflation following vessel puncture may occur.

Minor complications may include wound infection or hematoma, peritoneal irritation from retained intra-abdominal gas, subcutaneous emphysema, and vulvar edema. In contrast to these short-term problems, complications also may develop long after the surgery. Fortunately, incisional hernia formation following laparoscopy is infrequent, and trocar-site metastases develop uncommonly following cases in which malignancy is diagnosed.

In an attempt to identify risk factors for laparoscopic complications, Mirhashemi and co-workers (1998) found that increasing age and lower than average body mass index (BMI) were important factors. As noted earlier, complications also increase with the complexity of procedures performed.

Puncture Injuries

Because a sharp Verres needle and trocars may be used during laparoscopic entry, often blindly, risk for vessel and organ trauma is present. Risk factors have been identified, and these include intra-abdominal adhesions, insufficient gastric emptying, full bladder, insufficient pneumoperitoneum, poor muscle relaxation, thin patient habitus, and inappropriate angle or force of trocar insertion. As discussed below, several authors have advocated use of the open entry method as a means to lower rates of puncture injury (Catarci, 2001; Hasson, 2000; Munro, 2002).

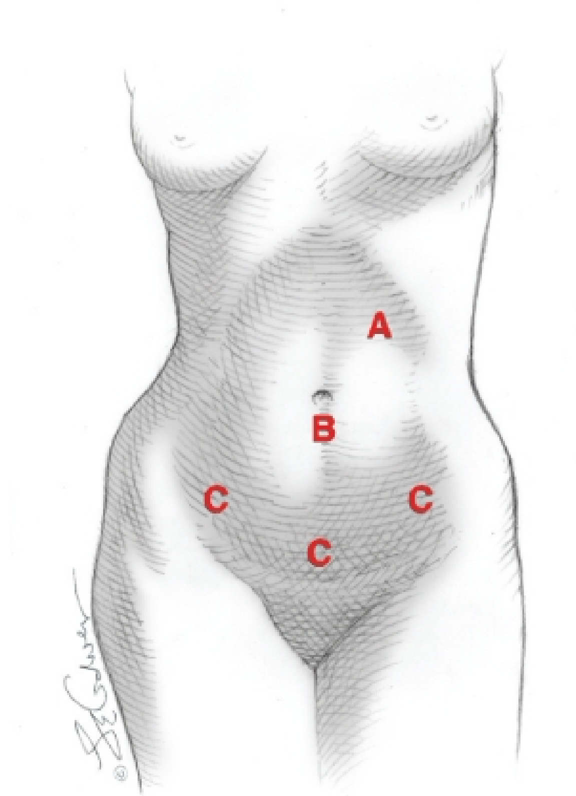
Bowel Injury

The most common type of organ injury during laparoscopy is bowel injury and has been cited as 0.6 and 1.6 per 1,000 cases (Chapron, 1999; Harkki-Siren, 1997b). Women with previous laparotomy have a higher incidence of abdominal adhesions and are at greatest risk for this complication.

Unfortunately, bowel injury sustained during laparoscopy is often missed at the time of surgery. For example, in an observational study by Chandler and co-workers (2001), nearly 50 percent of both small and large bowel injuries were unrecognized for 24 hours or longer. Typically, these patients present with fever, abdominal pain, nausea, and vomiting within 48 hours of surgery (Li, 1997).

Preventative steps to avoid bowel injury in those with risks for abdominal adhesive disease include: (1) use of the open entry technique, (2) umbilical introduction of a microlaparoscope to scout for adhesions, and (3) primary trocar entry in the left hypochondrium rather than at the umbilicus. Palmer described a closed entry method that places the primary laparoscopic trocar at a point in the left midclavicular line 3-cm caudal to the costal margin (Fig. 41-28.1). In this region, visceral-parietal adhesions were found rarely (Ternamian, 2006). Lastly, decompression of the stomach with an orogastric tube prior to Verres needle placement can assist in lowering the risk of stomach puncture (Philosophe, 2003).

FIGURE 41-28.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Abdominal access sites. **A.** Primary entry site in left upper quadrant entry at Palmer point. **B.** Primary entry site inferior to umbilicus. **C.** Accessory trocar sites.

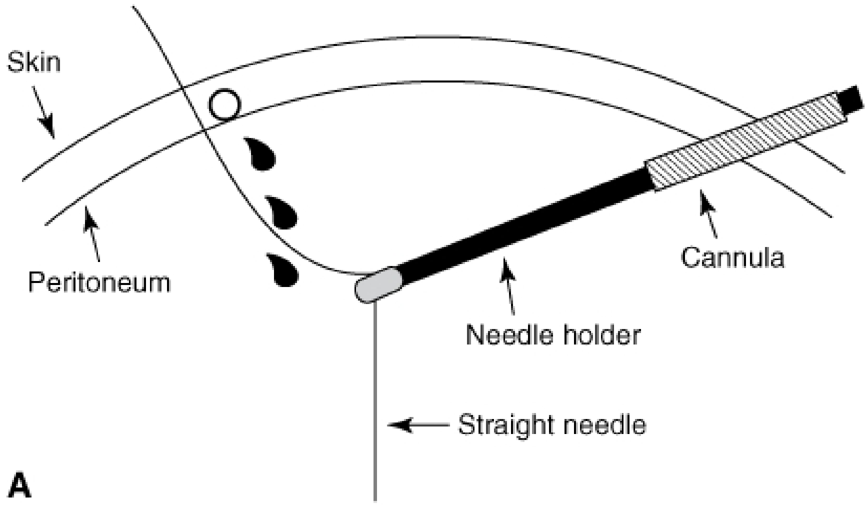
Vascular Injury

Major vascular injury associated with laparoscopy is rare and typically results during primary trocar insertion. Rates of injury have been cited as 0.09 to 5 per 1,000 cases, and characteristically, the terminal aorta, vena cava, and iliac vessels have been injured (Bergqvist, 1987; Bonjer, 1997; Catarci, 2001; Nordestgaard, 1995).

Although infrequent, a significant number of deaths result from large vessel injury (Baadsgaard, 1989; Munro, 2002). Prevention may include use of the open entry technique or awareness of the angle and force of trocar entry. Despite these steps, though, if a large vessel is punctured, the Verres needle or trocar should not be removed because it may act as a vascular plug. Laparotomy, direct manual pressure on the vessel, and notification of a vascular surgeon should follow.

In contrast, if the inferior epigastric artery is injured, several simple techniques can control hemorrhage. First, electrosurgical coagulation of the bleeding site may suffice in many cases. If this is unsuccessful in controlling bleeding, a 14F Foley catheter can be threaded through the cannula of the wounding trocar or through the defect created by this trocar. The Foley balloon then is inflated and pulled upward to create pressure against the posterior surface of the anterior abdominal wall. At the skin surface, a Kelly clamp is placed perpendicular across the Foley catheter and parallel to the skin to hold the balloon firmly in place. The balloon and catheter can be removed 12 hours later. Alternatively, Chatzipapas and Magos (1997) described a process that directs sutures from the skin surface through the abdominal wall and peritoneum to arch under the bleeding vessel to allow direct vessel ligation (Fig 41-28.2).

FIGURE 41-28.2



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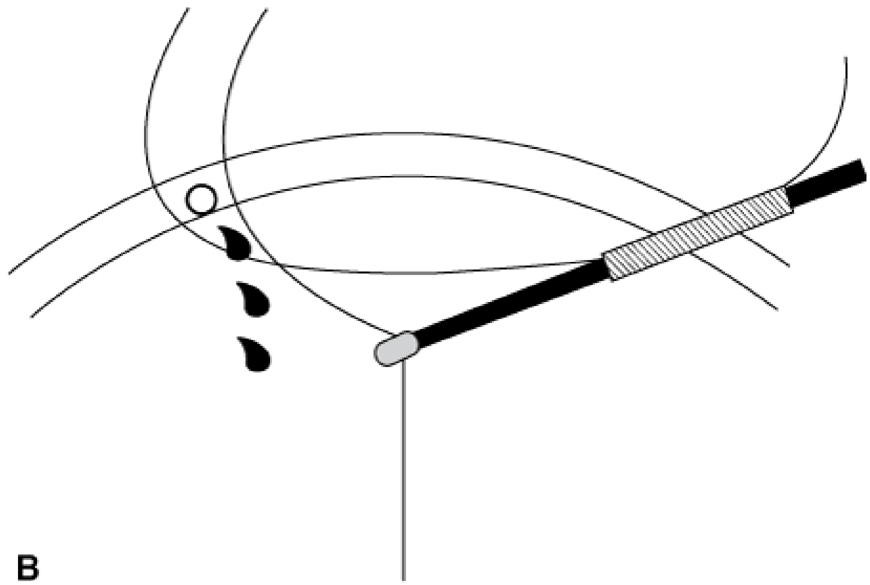

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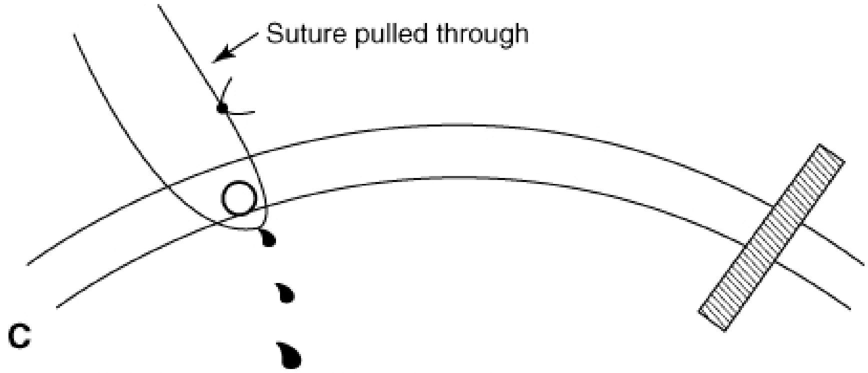

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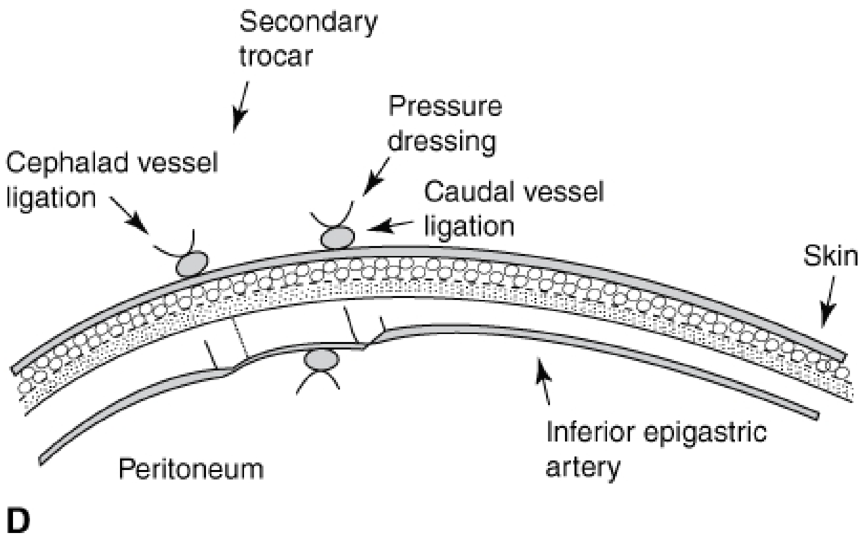


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

A. Suture with an attached straight needle is driven through the anterior abdominal wall lateral and caudal to the bleeding vessel. This is performed using direct laparoscopic visualization to avoid organ injury. A laparoscopic needle driver or atraumatic grasping forceps grabs the needle. Both needle and driver are drawn up and out of a contralateral cannula. **B.** A similar procedure is repeated medial and caudal to the bleeding vessel. **C.** The needles are cut from the two suture strands and are tied together outside the abdominal cavity. The knot is dragged back through the cannula. This creates a suture sling caudal to the point of vessel bleeding. **D.** Both suture strings then are tied again outside the abdomen over a pressure dressing to occlude the caudal portion of the inferior epigastric vessel. The entire process is repeated cephalad to the bleeding vessel. (Modified from Chatzipapas, 1997, with permission.)

Urinary Tract Injury

Bladder puncture is an uncommon risk of laparoscopy, but with the increasing use of laparoscopic hysterectomy techniques, rates of ureteral injury have increased. Bladder decompression prior to and during surgery and careful placement of secondary trocars will prevent many cases of injury.

Thermal Injury

Electrosurgical complications may lead to accidental burns by direct contact of the instrument or by stray electric current. Fortunately, the risk of this complication is low. For example, Meikle and co-workers (1997) noted a thermal bowel injury rate of 4 per 1,000 laparoscopically assisted vaginal hysterectomy (LAVH) cases. In addition to the bowel, thermal injury also can lead to

ureteral stricture and urinary tract fistula formation.

Steps to avoid these injuries include keeping instrument tips within the visual field when electric current is applied, strict instrument maintenance to identify insulation defects, employment of bipolar coagulation for hemostasis when feasible, and use of lower-voltage (cutting) current whenever possible to reduce the applied voltage (Wu, 2000).

Incisional Hernia

Incisional hernias have been described as a potential long-term consequence of laparoscopy. The incidence approximates 1 percent but may rise in the future with the increasing use of larger trocars for operative laparoscopy. Approximately one fourth of hernias are umbilical, and the remainder develop at secondary trocar sites (Lajer, 1997).

A major risk for this complication is the use of large trocars measuring 10 mm or greater in diameter. Accordingly, to reduce the frequency of these hernias, it is recommended to use smaller trocars when possible and to use a fascial suture closure at larger trocars wound sites. Similarly, the use of conical tipped trocars as opposed to pyramidal trocars has shown to lower this incidence (Leibl, 1999). Finally, care should be taken to ensure that peritoneal tissue is not drawn into the trocar canals when removing the cannulas (Boughey, 2003; Montz, 1994).

Trocar-Site Metastasis

Rates of trocar-site cancer metastasis are low and complicate the clinical course of approximately 1 percent of patients in whom gynecologic malignancy is identified (Childers, 1994). Although most trocar-site metastases are associated with advanced stages of disease, metastasis has followed surgery for tumors of low malignant potential. As a result, the components of laparoscopy itself have been evaluated as a risk for tumor spread to the trocar sites (Ramirez, 2004). Currently, no evidence-based consensus addresses prevention of this complication.

PATIENT PREPARATION

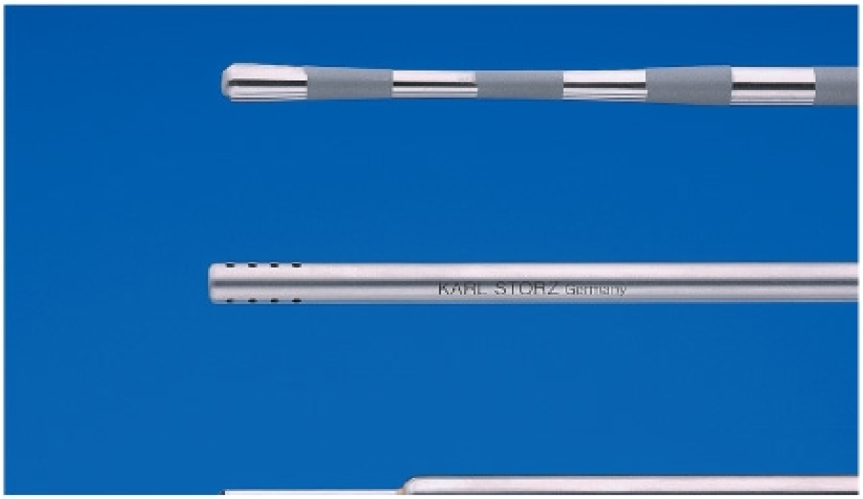
Overall, laparoscopy has been associated with lower rates of postoperative infection than laparotomy. Therefore, the decision to administer antibiotics with laparoscopic procedures is influenced by the procedure itself and not the approach.

Intraoperative

INSTRUMENTS

Because of the small incisions employed with laparoscopy and the increased distance between surgeons and their operative field, specialized instruments have been developed (Fig. 41-28.3).

FIGURE 41-28.3



A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

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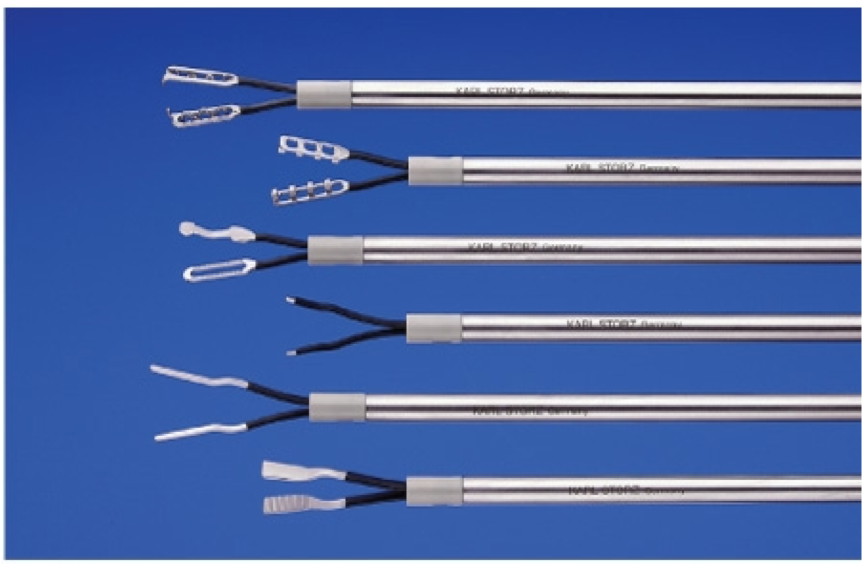


D

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

A. From top to bottom, blunt probe, suction-irrigation probe, needle for puncture. **B.** Laparoscopic scissors and grasping forceps. **C.** Grasping forceps. **D.** Bipolar forceps. (Courtesy of Karl Storz America, Inc.)

Uterine Manipulator

During laparoscopy, manipulation of the uterus allows improved visualization of cul-de sac structures and aids in creating countertraction on lateral pelvic structures during operative procedures. For this purpose, a uterine manipulator is placed into the endocervical canal or endometrial cavity. Several types of manipulators have been designed, but the uniting principle is a rigid,

hollow-bore device whose cephalad end is inserted into the endocervical canal or endometrial cavity and whose stiff caudal stem spans the vagina and exits the introitus to allow manipulation by the surgeon or assistant. Additionally, the device's hollow bore permits chromotubation (Figs. 41-28.4 and 41-28.5).

FIGURE 41-28.4

A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Cohen cannula. This device is used in conjunction with a separate tenaculum. The tenaculum is placed horizontally on the anterior cervical lip. **A.** The narrow cephalad tip of the cannula fits into the endocervical canal. The conical head abuts the external cervical os and limits insertion into the endometrial cavity. **B.** The caudad portion contains a crossbar into which the ratched handle of the cervical tenaculum fits.

FIGURE 41-28.5

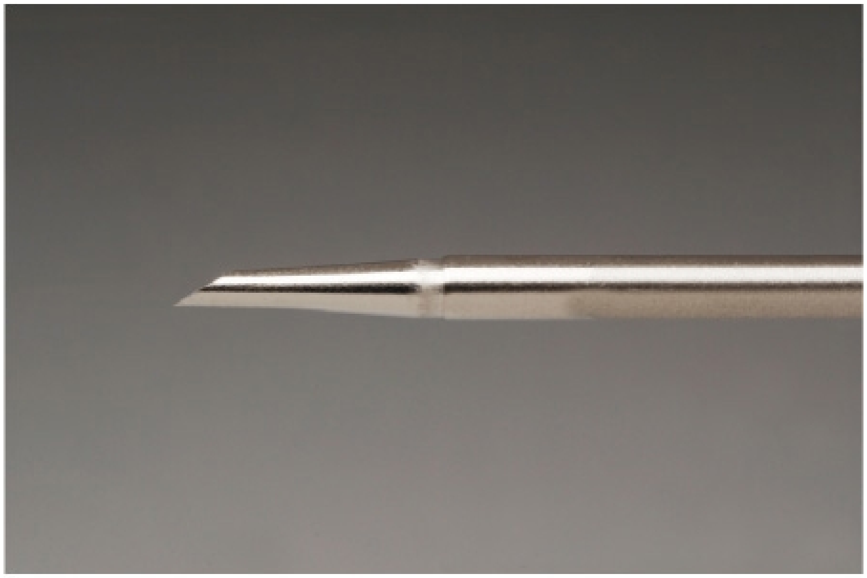
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

A balloon-type uterine manipulator. The deflated balloon tip is inserted into the endometrial cavity. The balloon is inflated to hold the stiff manipulator in place.

Verres Needle

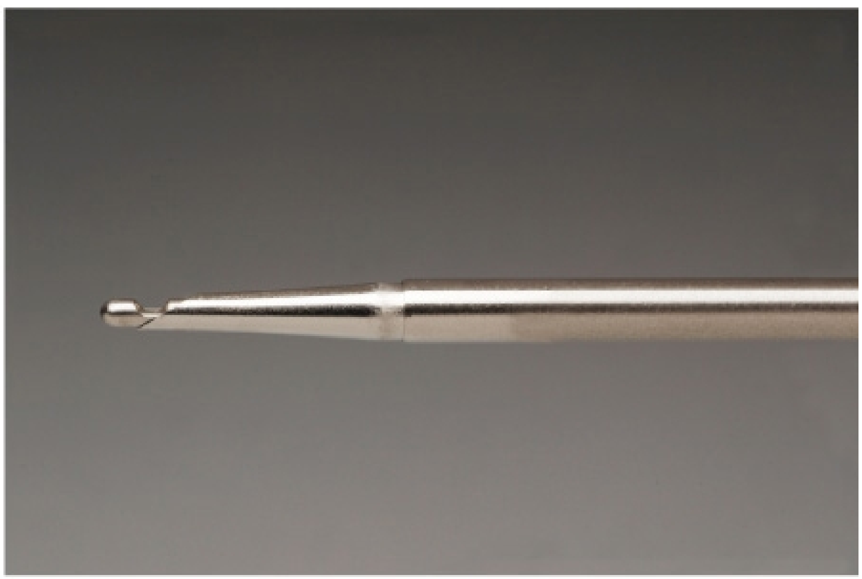
Several techniques can be used to initially enter the abdominal cavity. The most common method employed by gynecologists uses a long, slender needle, called a *Verres needle,* to conduct gas into the abdomen and create a pneumoperitoneum (Fig. 41-28.6). The pressure and peritoneal tenting created by this gas aid entry of the first trocar.

FIGURE 41-28.6



A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

The Verres needle consists of a sharp outer needle **A.** which houses a blunt-tipped, spring-loaded inner stylet **B.** (Courtesy of Ethicon.)

With insertion of the Verres needle, tissue resistance compresses an inner spring, and a blunt stylet, which is slightly longer than the sharp external needle sheath, retracts. The stylet remains retracted until the sharp tip of the external needle sheath pierces the peritoneum. At this point, tissue resistance disappears, and the blunt stylet is pushed forward by the inner spring to prevent organ or vessel injury. This self-retracting concept is seen again in the design of disposable trocars with retractable shields.

Abdominal Trocars

Trocars are used gain access to the abdominal cavity. First-generation trocars consist of a hollow, long, slender cannula that sheaths an inner stylet. Trocars typically range from 5 to 12 mm in diameter, and their tips may be either conical, pyramidal, or blunt (Fig. 41-28.7).

FIGURE 41-28.7

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Trocars consist of outer cannula and inner obturator. The trocar is used to gain access to the abdomen. The obturator then is removed, and the cannula serves as a conduit through which to introduce instruments. Obturators may have a pyramidal (top), conical (middle), or blunt tip (bottom). (Courtesy of Karl storz America, Inc.)

Conical trocars are smooth except for their pointed tip and therefore have no cutting edges. They split the fascia rather than cut it and thus are preferred by some to lower the risk of vessel injury and postoperative hernia formation (Hurd, 1995; Leibl, 1999). They require more penetration force to insert, however. In contrast, pyramidal trocars have sharp edges and tip and as result, cut the fascia as they are inserted into the abdomen.

In the 1980s, trocars with retractable shields were introduced. Similar, to the concept used with the Verres needle, a hollow plastic retractable shield covers the trocar tip both before and after the trocar pierces the abdominal wall. In this manner, the cutting edge is exposed only during its passage through the fascia. Despite theoretical advantages to these shielded trocars in preventing organ injury, studies have failed to show their superiority (Fuller, 2003).

Suction-Irrigation Systems

During laparoscopic procedures, irrigation and suctioning of electrosurgical smoke, blood, or irrigation fluids is often required. For this reason, suction-irrigation systems have been developed to offer both modalities through a 5-mm hollow-bore rod (see Fig. 41-28.2A).

Specimen Bags

Certain surgeries such as ovarian cystectomy require removal of specimens in a manner that minimizes contamination of these specimens or their contents to the operating field. Accordingly, purse-string endoscopic bags have been developed (Endo Catch,

Auto Suture, Norwalk, CT; Endosac, Zenith Medical, SanDiego, CA) (Fig. 41-28.8).

FIGURE 41-28.8

A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

C

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Endoscopic bag. (Courtesy of Ethicon.)

Electrosurgery

Suture ligatures for hemostasis are more difficult to apply during laparoscopy. Accordingly, electrosurgical coagulation takes on added importance, and both unipolar and bipolar modalities can be used. A fuller discussion of electrosurgical principles can be found in Chapter 40, Electrosurgery.

Disposable versus Reusable

The instruments just described are available in both reusable and disposable forms, each having its own advantages. The main advantage to reusable instruments is lowered expense. Cost analyses have demonstrated that disposable instruments add significant cost compared with reusable ones (Campbell, 2003; Morrison, 2004).

The main advantage to disposable instruments stems from the consistent sharpness of laparoscopic Verres needles, trocars, and scissors and from avoidance of lost instrument parts. For example, Corson and associates (1989) showed that reusable trocars, although sharpened at regular intervals, still required twice the force for entry compared with disposable trocars. Dull scissors may lead to longer operating times and ineffectual surgical technique. As a result, these advantages and disadvantages must be balanced when selecting either a reusable or disposable instrument with laparoscopy.

Carbon Dioxide Insufflation

Carbon dioxide (CO_2) is currently the insufflation gas of choice for laparoscopy. It fulfills most of the requirements for an ideal insufflation gas, being colorless, noninflammable, and rapidly excreted from the circulation. However, disadvantages include CO_2 absorption across peritoneal surfaces into the circulation; constant gas leaks, which prolong surgery; and peritoneal irritation due to conversion of CO_2 to carbonic acid. Moveover, retained intra-abdominal gas can lead to diaphragmatic irritation and referred neck and shoulder pain postoperatively.

To counter these potential problems with CO_2 use, gasless laparoscopy has been described. This technique uses a device with fan bladeâ€"shaped retractors attached to the end of a rod. The blades of the device are placed along the peritoneal surface of the anterior abdominal wall, and the rod extends up through the umbilical incision. An electric lift attaches to the rod and elevates the anterior abdominal wall. As opposed to the dome shape created by a pneumoperitoneum, gasless devices create a truncated pyramidal shape.

Despite advantages, drawbacks with gasless laparoscopy currently limit its routine use, although it still may have value in high-risk patients with cardiorespiratory diseases (Cravello, 1999; Goldberg, 1997; Negrin Perez, 1999).

Surgical Steps

1. **Anesthesia and Patient Positioning.** Most laparoscopic surgery is performed in an operating room and requires general anesthesia. Some investigators, however, have described in-office microlaparoscopy using 2- to 3-mm microlaparoscopes for such diverse uses as second-look evaluation of cancer treatment, sterilization, and pelvic pain and infertility evaluation (Franchi, 2000; Kovacs, 1998; Mazdisnian, 2002; Palter, 1999).

   For the anesthesiologist, patient positioning and gases used for abdominal insufflation can create specific concerns. For example, Trendelenburg positioning of the patient enables bowel repositioning for the surgeon. But as a result of increased pressure against the diaphragm by abdominal contents, ventilation may be more difficult. Similarly, distention of the abdominal cavity with CO_2 gas under pressure also can add to ventilatory resistance. Another concern with the distending medium stems from its absorption into the bloodstream. Depending on the length of the operation, significant volumes of CO_2 can be absorbed and lead to hypercarbia. A final consideration is gastric decompression, and an orogastric tube is recommended by many. This preventative measure decreases the risk of stomach puncture by the Verres needle or trocar during their insertion (Chapron, 1999).

   Once adequate anesthesia has been delivered to allow manipulation of the uterus, the patient is placed in a dorsal lithotomy position. Correct patient positioning is critical to avoiding nerve injury, which and is discussed in Chapter 40, Patient Positioning. The vagina and abdomen should be surgically prepped and the bladder drained. If a longer procedure is anticipated, a Foley catheter may be required because a full bladder can obstruct the operating view and increase the risk of bladder injury.

2. **Uterine Manipulator Placement.** The surgeon is double gloved to allow placement of the uterine manipulator. Vaginal retractors are used to display the cervix, and a single-toothed tenaculum is placed on the anterior cervical lip. A Cohen uterine manipulator then is inserted into the external cervical os. Alternatively, the balloon end of an endometrial cavity manipulator may be threaded into the endometrial cavity. The outer pair of surgical gloves is removed, and the surgeon moves to one side of the patient.

3. **Primary Trocar Entry.** There are four basic techniques to place the trocar that will house the laparoscope: (1) Verres needle insertion, (2) direct trocar insertion, (3) optical access insertion, and (4) open entry methods. The first three are classified as *closed entry* techniques in contrast with the *open entry* method.

   Closed entry techniques offer quick access to the abdominal cavity with a low risk of complications (Bonjers, 1997; Catarci, 2001). These techniques are best performed with supine patients lying in a horizontal plane. Although most gynecologic laparoscopy is performed with patients in the Trendelenburg position, this position is dangerous for the initial entry portion of the procedure. In Trendelenburg position, the aortic bifurcation lies directly below the umbilicus and thus is more vulnerable to puncture.

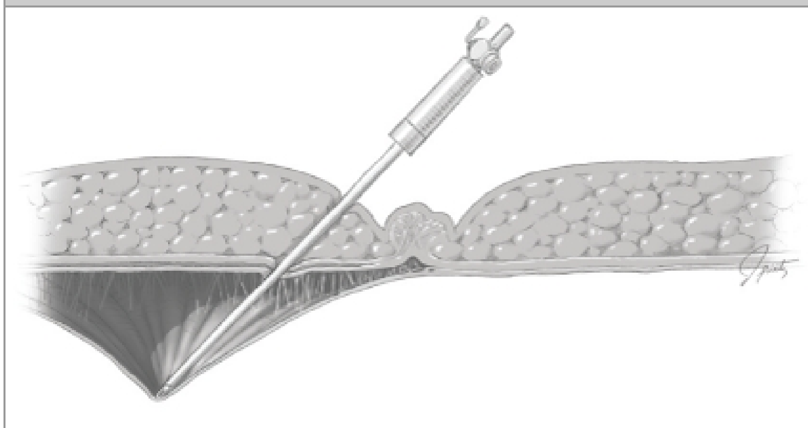
   In most cases, the umbilicus is chosen as the site of entry because it is relatively avascular and the thinnest accessible portion of the anterior abdominal wall (see Fig. 38-2). An incision that will accommodate the laparoscopic trocar should be made along Langer lines for best cosmetic results. These lines reflect the natural skin tension lines created by arrangement of underlying skin collagen.

4. **Verres Needle Entry.** Entry using a Verres needle is a two-step process. First, the Verres needle tip is placed intra-abdominally to allow partial insufflation of the abdomen. Then puncture of the fascia and the peritoneum follows with a larger trocar.

   Prior to needle placement, the anterior abdominal wall is elevated by grasping the wall caudal to the umbilicus with one hand. This distances the abdominal wall from the intra-abdominal contents by 6 to 8 cm. If the patient is overweight, two towel clamps can be used on each side of the umbilicus to achieve a similar effect.

   The Verres needle is inserted at a 45-degree angle from vertical and is directed along the midline toward the pelvis (Fig. 41-28.9).

FIGURE 41-28.9



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Verres needles tenting the peritoneal layer.

5. **Placement Confirmation.** Entry failure with this method usually stems from placement of the Verres needle tip in the preperitoneal space rather than within the abdominal cavity. Therefore, confirmation of intra-abdominal positioning prior to gas instillation is critical. For confirmation, 10 mL of saline can be injected through the needle following placement. Injection with an inability to re-aspirate the fluid is presumptive of correct placement. Similarly, if a drop of saline that has been placed on the external end of the Verres needle is sucked quickly into the abdominal cavity, then correct placement is likely.

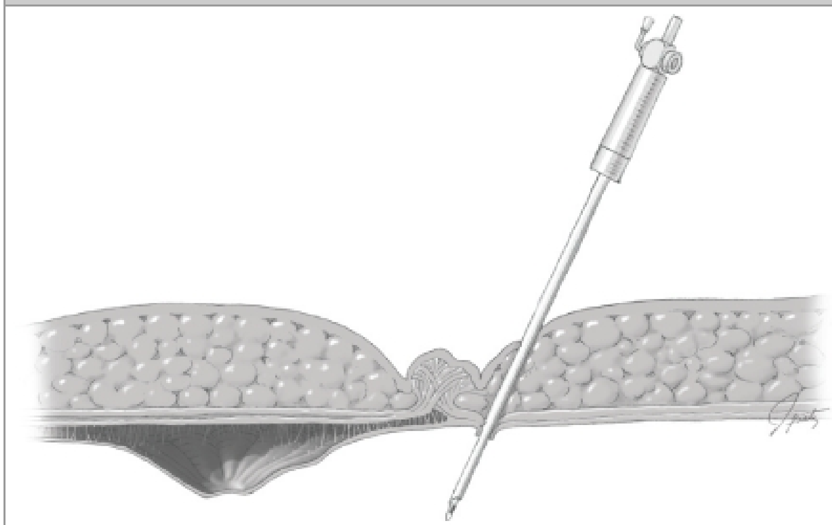
6. **Gas Insufflation.** Following needle puncture and placement verification, the abdomen is insufflated with CO_2 to reach an intra-abdominal pressure of 10 to 12 mm Hg. In many patients, this correlates with an infusion of 2.5 to 3 L of gas.

7. **Primary Trocar Insertion.** The Verres needle is removed, the abdominal wall below the umbilicus is manually elevated, and a trocar is placed in the umbilical incision. The insertional angle of this trocar mirrors that of the Verres needle. The trocar punctures the fascia and underlying peritoneum and enters the abdominal cavity. A gas rushing sound characteristically confirms placement.

8. **Abdomen Insufflation.** The abdomen then is further insufflated as needed. A constant intra-abdominal pressure of 10 to 15 mm Hg is optimal for laparoscopy. Higher pressures can result in ventilatory difficulties. With most equipment in use today, a surgeon can set a maximal abdominal pressure beyond which flow of gas ceases automatically.

9. **Incorrect Needle Placement.** Failures can occur with this method and stem from incorrect needle placement with creation of preperitoneal emphysema (see Fig. 41-28.9). This gaseous dissection of the peritoneum away from the anterior abdominal wall hinders the trocar in piercing the peritoneum. Instead, the trocar further stretches and pushes the peritoneum internally. This problem fortunately often can be overcome by a second attempt with the Verres needle above the umbilicus (Fig. 41-28.10).

FIGURE 41-28.10



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Verres needle replacement above the umbilicus.

10. **Direct Trocar Entry.** Because of entry failures associated with preperitoneal insufflation, a direct entry method was evaluated subsequently (Copeland, 1983; Dingfelder, 1978). The procedure involves lifting the abdominal wall and directly piercing and entering the anterior abdominal wall without prior insufflation.

    Several comparative studies between Verres needle and direct trocar techniques have shown lower rates of entry failure with the direct method (Byron, 1993; Clayman, 2005; Gunenc, 2005). Moreover, these investigators found comparable or lower associated minor complication rates with direct trocar entry.

11. **Optical Access Trocar Entry.** To lower the risk of bowel injury at the time of primary trocar insertion, optical trocars were developed in the early 1990s. These devices, in essence, combine the laparoscope and trocar into one tool. During use, the optical trocar transmits images of the abdominal wall layers to a television monitor. These layers then are cut under direct visualization by advancement of the sharp trocar edge.

    Despite the theoretical advantage to this type of trocar, major organ injury still has been reported with use of optical access trocars. Moreover, no large studies have been performed to establish its clinical superiority over other closed entry techniques (Sharp, 2002).

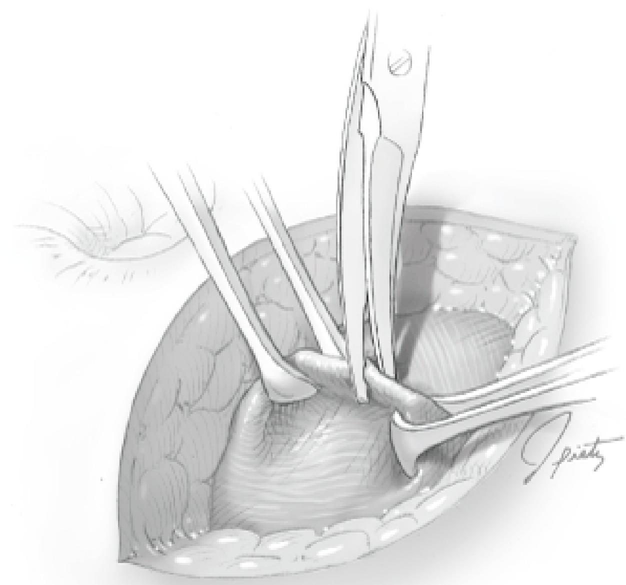
12. **Open Entry.** Because of associated risks of puncture injury with the closed entry techniques, an open entry technique was described by Hasson (1971, 1974). This technique requires use of a trocar composed of a blunt-tipped obturator that is sheathed by an outer cannula. It is recommended by many surgeons for patients with prior abdominal surgery, for those following a closed technique entry failure, and for pediatric patients (Madeb, 2004).

    In a retrospective review of more than 5,000 open entry procedures, Hasson and associates (2000) noted that minor and medium-risk complications developed at a rate of 0.5 percent. Moveover, in studies comparing open and closed techniques, open methods showed lower rates of entry failure and organ injury (Bonjers, 1997; Merlin, 2003). This technique, however, is not foolproof, and organ injury, mainly bowel, has been described (Magrina, 2002). Typically, this method of entry takes longer than closed entry, and the pneumoperitoneum can be difficult to maintain in some cases due to air escape from around the cannula.

13. **Umbilical Incision for Open Entry.** A 1- to 2-cm transverse incision at the lower edge of the umbilicus is made while applying tension with fine-toothed forceps to its lateral borders. Skin edges are retracted laterally to expose the linea alba, and the fascia is dissected free of adhesions and adipose tissue.

    The fascia is lifted and everted upward with two Allis clamps (Fig. 41-28.11). A 0.5- to 1-cm incision with scalpel or scissors then transects the fascia. The Allis clamps are repositioned, one on each free fascial edge.

FIGURE 41-28.11

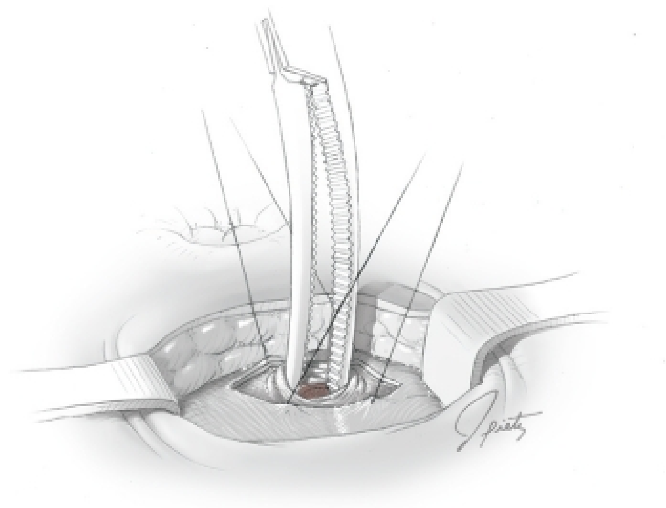


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Fascial incision for open entry.

14. **Peritoneal Entry.** A hemostat or finger is used to bluntly open the peritoneum, and the end of an S-shaped retractor is placed into the abdomen. The abdominal portion of the retractor is used to shield the underlying organs as a stitch of 0-gauge delayed-absorbable suture is place parallel on one side of the fascial opening (Fig. 41-28.12). This suture is not tied. This suturing step is repeated on the opposite fascial edge.

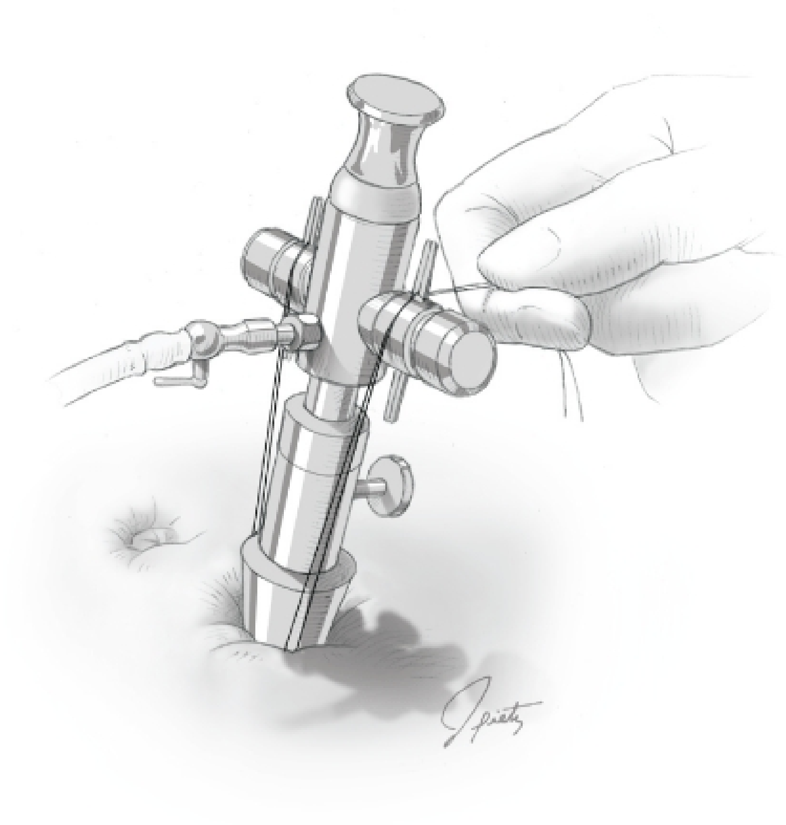
FIGURE 41-28.12



Peritoneal entry during open entry.

15. **Primary Trocar Placement with Open Entry.** The distal, blunt end of the trocar then is inserted into the incision. The fascial tag sutures are pulled firmly upward and threaded into the suture holders found on either side of the cannula's proximal end (Fig. 41-28.13). The blunt obturator is removed, and the laparoscope is threaded through the cannula.

FIGURE 41-28.13



Primary trocar placement with open entry.

16. **Secondary Operative Cannula Site Selection.** During laparoscopy, additional operative cannulas are needed to insert instruments into the abdomen. The number, location, and size of these cannulas will vary depending on the surgical instruments required for the laparoscopic procedure.

    The patient is placed in Trendelenburg position to aid displacement of bowel from the pelvis. Trocars are placed using direct laparoscopic visualization to minimize the puncture risk to anterior abdominal wall vessels or to the bladder. Typical cannula sites are displayed in Figure 41-28.1.

17. **Transillumination.** Within the anterior abdominal wall, the superficial and inferior "deep" epigastric arteries course parallel to the rectus abdominis muscles (see Fig. 38-3). Specific to avoiding puncture of the superifical epigastric vessels, transillumination of the anterior abdominal wall is useful. During this process, the laparoscope, within the abdominal cavity, is placed directly against the peritoneal surface of the anterior wall. The wall is illuminated, and the superficial epigastric arteries are seen as dark vessels traversing it.

18. **Inferior Epigastric Artery Indentification.** Unfortunately, the inferior epigastric arteries lie deep to the rectus abdominis muscle and are poorly seen with transillumination (Hurd, 1992). These arteries, however, can be seen by direct laparoscopic visualization in most cases (Hurd, 2003). Anatomic landmarks also can be used to avoid vessel puncture. For example, using results from cadaveric dissection, Epstein and co-workers (2004) noted that the main stem of the inferior epigastric artery can be avoided if trocars are inserted within the lateral third of the distance between the midline and anterosuperior iliac spine.

19. **Laparoscopic Procedures.** The indicated procedure then may be performed.

20. **Abdomen Deflation.** At completion of laparoscopy, the abdominal cavity is deflated. To prevent diaphragmatic irritation from retained CO_2 , manual pressure should be placed on the abdomen to help expel remaining gas.

21. **Trocar Removal at Surgery's End.** On completion of surgery, cannulas should be removed using laparoscopic visualization. This allows evaluation for bleeding from punctured vessels that may have been tamponaded by the cannula. Additionally, it prevents herniation of bowel or omentum up through the cannula track and into the anterior abdominal wall.

22. **Closed Entry Incision Closure.** Depending on their size, incisions may require deep fascial stitches. Lajer and co-workers (1997) recommended fascial closure to prevent incisional hernia formation whenever trocars measuring 10 mm or greater were used. Skin incisions are closed with a subcuticular stitch of 4-0 delayed-absorbable suture. Alternatively, the skin may be closed with cyanoacrylate tissue adhesive (Dermabond Topical Skin Adhesive, Ethicon, Somerville, NJ) or skin tape (Steri-Strip Elastic with Steri-Strip Compound Benzoin Tincture, 3M HealthCare, St. Paul, MN).

23. **Open Entry Incision Closure.** During removal of the Hasson trocar, sutures originally placed in the fascia are unthreaded from the trocar. Each of these sutures then is brought to the midline of the incision, and square knots are tied to close the fascial defect. The skin is reapproximated using a subcuticular suture with 4-0 delayed-absorbable suture (Hasson, 2000).

Postoperative

Depending on the procedure performed, most patients can be discharged home on the same day as surgery. For most, physical activities and diet can be resumed based on patient comfort.

41-29 LAPAROSCOPIC STERILIZATION

Approximately 700,000 tubal sterilization procedures are performed annually in the United States. About half of these follow pregnancy delivery or termination, but the others are performed independent of pregnancy and are termed *interval sterilization* (Westhoff, 2000). Most interval procedures are performed laparoscopically, and most commonly involve tubal occlusion by electrosurgical coagulation, by mechanical clips, by Silastic bands, or by suture ligation (Pati, 2000).

Preoperative

CONSENT

Tubal sterilization is a safe surgical procedure with few associated complications. In general, the risks of laparoscopic sterilization mirror those of laparoscopy, as discussed in Section 41-28, Laparoscopy. Rarely, case reports of clip migration to sites such as the bladder, uterine cavity, and anterior abdominal wall have been noted in the literature (Gooden, 1993; Kesby, 1997; Tan, 2004). Most ectopic clips are incidental findings with untoward patient effects, but less commonly, they can incite local foreign-body reactions.

In addition to surgical risks, contraceptive failure and pregnancy rates related to each procedure should be discussed with patients (see Chap. 5, Sterilization). Overall, these rates are low, and tubal sterilization is an effective method of contraception. For this reason, patients undergoing this procedure should be confident in their desires for permanent sterilization.

If pregnancy does occur, however, there is a greater risk of ectopic pregnancy. Bipolar coagulation has the highest risk for this complication compared with that of clips and bands (Peterson, 1996). Accordingly, amenorrhea following any sterilization procedure should prompt serum β-hCG testing to aid in identifying ectopic pregnancies.

Lastly, a small percentage of women experience regret following sterilization (see Chap. 5, Cautions). For this reason, prior to surgery, women should be counseled about the risk of regret and about alternative effective long-term contraceptive methods.

Intraoperative

Surgical Steps

1. **Anesthesia and Patient Positioning.** Most laparoscopic tubal sterilization procedures are performed using general anesthesia, although a few investigators have described microlaparoscopic procedures using local or regional analgesia (Siegle, 2005; Tiras, 2001).

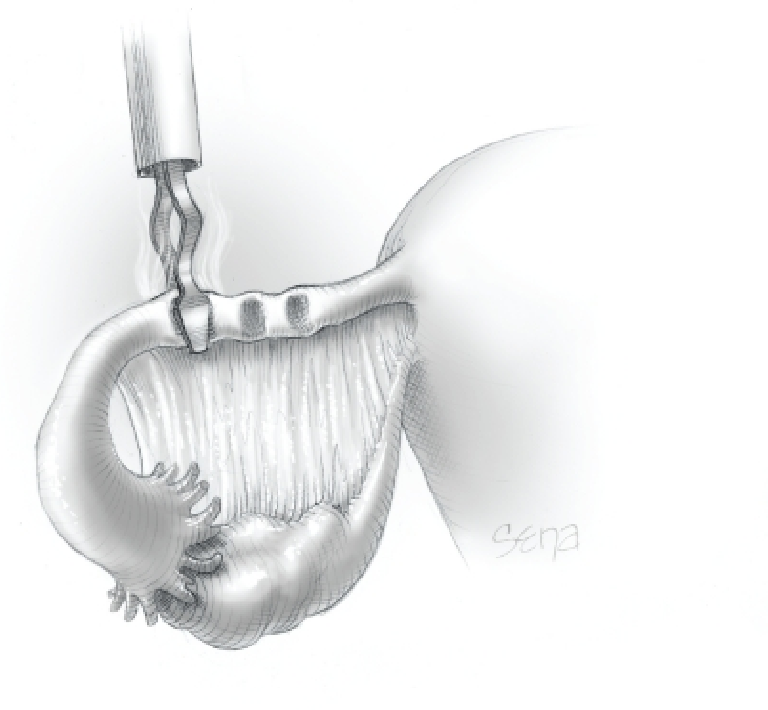
   In patients receiving general anesthesia, investigators also have evaluated the adjunctive use of several local analgesia techniques. Specific to sterilization procedures, 5 mL of a 0.25-percent or 0.5-percent bupivacaine solution from a needle and syringe may be dripped onto the serosal tubal surface prior to tubal occlusion (Brennan, 2004; Wrigley, 2000). Most studies comparing outcomes both with and without this topical analgesia have shown improvement in pain scores during the immediate postoperative period (30 minutes to 1 hour) but no overall differences in pain scores at later time intervals or total pain medication consumption.

   Alternatively, bupivacaine solutions have been delivered transcervically through balloon laparoscopic uterine manipulators into the fallopian tube lumen (see Fig. 41-28.5). In most evaluations, however, this method has proved ineffective in lessening postoperative pain (Ng, 2002; Schytte, 2003).

   The patient is positioned in the dorsal lithotomy position, and for all the procedures described, the initial steps of laparoscopic abdominal entry are performed as described in Section 41-28, Laparoscopy.

2. **Bipolar Electrosurgical Coagulation.** The fallopian tube is identified and grasped in the isthmic region at least 2 to 3 cm lateral to the cornua (Fig. 41-29.1). Placement here is important. Pressure from retrograde menstrual flow against a coagulated stump that has been placed too close to the cornua can increase the risk of stump recanalization and fistula formation. Leaving a 2- to 3-cm segment allows ample space for absorption of intrauterine fluid without creating excess pressure against the stump.

FIGURE 41-29.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Bipolar electrosurgical coagulation.

3. **Electrocoagulation.** The coagulating paddles of bipolar forceps should span the tube. Overextending their grasp may lead to partial coagulation of the mesosalpinx and incomplete coagulation of the entire tube width.

   Before current is applied, the tube is elevated slightly and pulled away from other adjacent structures to prevent thermal injury to those structures. As current is applied, the tube will swell, and fluid often bubbles and pops from the tissue. Current is delivered until the tube is completely desiccated. Failure to reach this endpoint has been linked with increased contraceptive failures (Soderstrom, 1989). Because visual inspection of a tube typically is inadequate to assess complete desiccation, an ammeter is incorporated with most bipolar generators. Water conducts current through tissues, and completely desiccated tissue therefore are unable to conduct current. Accordingly, current should be applied until zero current flow across the tube is registered by the ammeter. Then the tube is released.

   A second site that is lateral to but contiguous with the first coagulated segment is grasped and similarly coagulated. A total of two to three contiguous sites are serially coagulated. This occludes a total span of 3 cm along the length of the tube. Coagulation of shorter distances along the tube can lead to recanalization and contraceptive failure (Peterson, 1999). These steps then are repeated on the opposite fallopian tube.

   Occasionally, following coagulation, the tube may stick to the bipolar paddles. To free the tube, slowly open the paddles and gently twist the forceps paddles to the right and then the left.

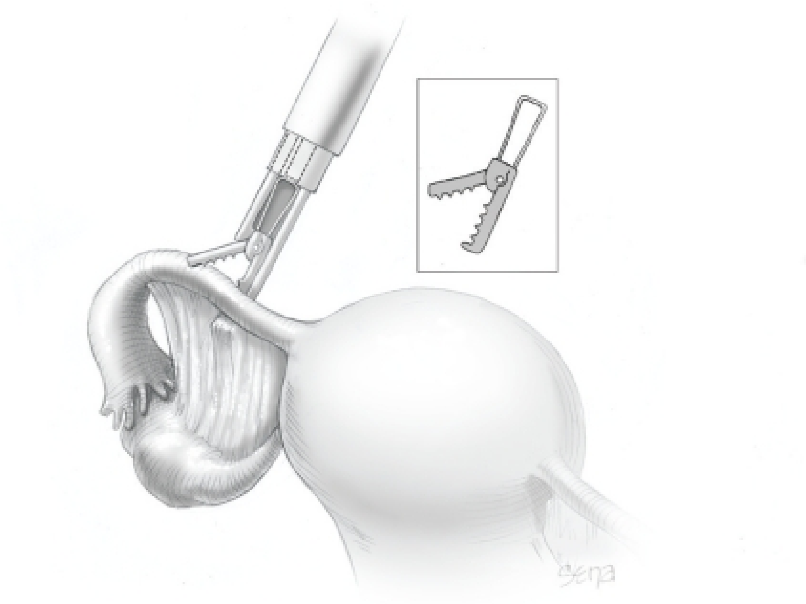
4. **Hulka Clip Application.** The plastic Hulka clip (Richard Wolf Medical Instruments Corporation, Vernon Hills, IL) is also generically known as a *spring clip* because of the metal spring that locks the clip into place during application.

5. **Clip Loading.** At the beginning of clip application, the trigger of the applicator is gently squeezed by the surgeon's thumb. This action advances the first arm of the applicator down and over the top of the clip. This closes the jaws of the clip to within 1 mm of each of other. This is an unlocked position yet allows the clip and applicator to be threaded down the laparoscopic cannula.

6. **Clip Application.** Once inside the abdomen, the applicator trigger is drawn backward, and the upper jaw of the clip reopens. The fallopian tube is grasped with atraumatic grasping forceps and outstretched horizontally and laterally. Concurrently, a uterine manipulator can be used to tilt the uterus laterally and in the opposite direction.

   Held within the applicator bracket, the clip is positioned across the narrow isthmic area of the tube, about 2 cm from the cornua, and perpendicular to the long axis of the tube (Fig. 41-29.2). The jaws are positioned around the tube in a manner that directs the tube deeply into the crux of the jaws. This aids in total occlusion of the tube as it is flattened across the base of the closing clip. Additionally, positioning of the distal tip of the applicator and clip should be such that when closed, the clip should incorporate a small portion of subjacent mesosalpinx.

FIGURE 41-29.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Hulka clip application.

7. **Clip Closure.** Once the applicator jaws are positioned appropriately, the thumb-action trigger is squeezed slowly to push forward the outer applicator arm and close the clip around the tube (Fig. 41-29.3). The clip application in inspected to ensure that it has encompassed the tube completely.

   If placement is deemed correct, the trigger is depressed fully. This forces the second arm forward against the butt of the clip's metal spring (Fig. 41-29.4). The band is pushed out and around the plastic frame of the clip to compress and lock the upper and lower clip jaws in place.

   One clip is placed on each tube. If a clip is misapplied, a second clip can be placed lateral to the first.

FIGURE 41-29.3

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Hulka clip closure.

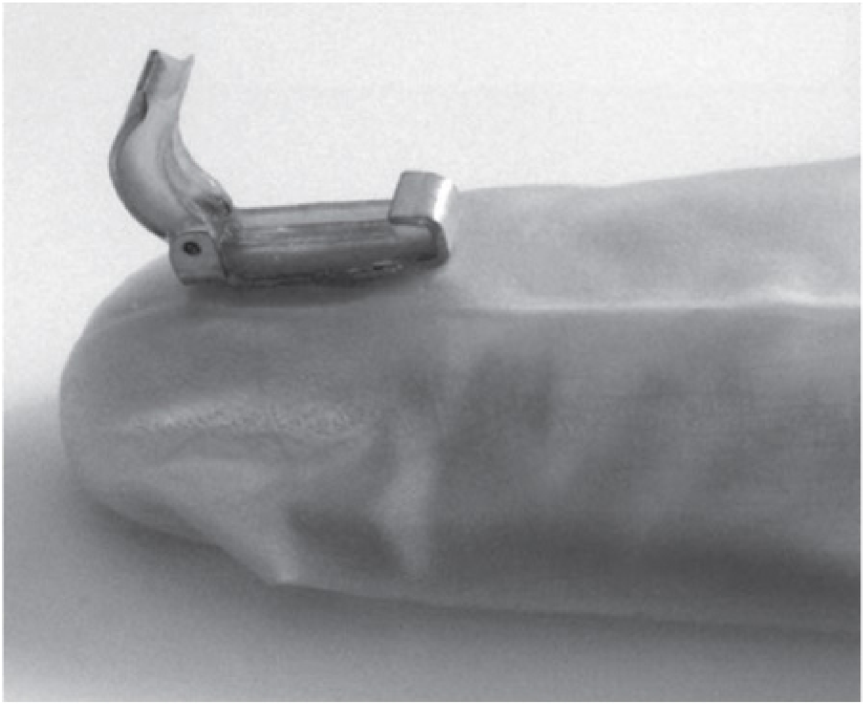
FIGURE 41-29.4

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Hulka spring secured.

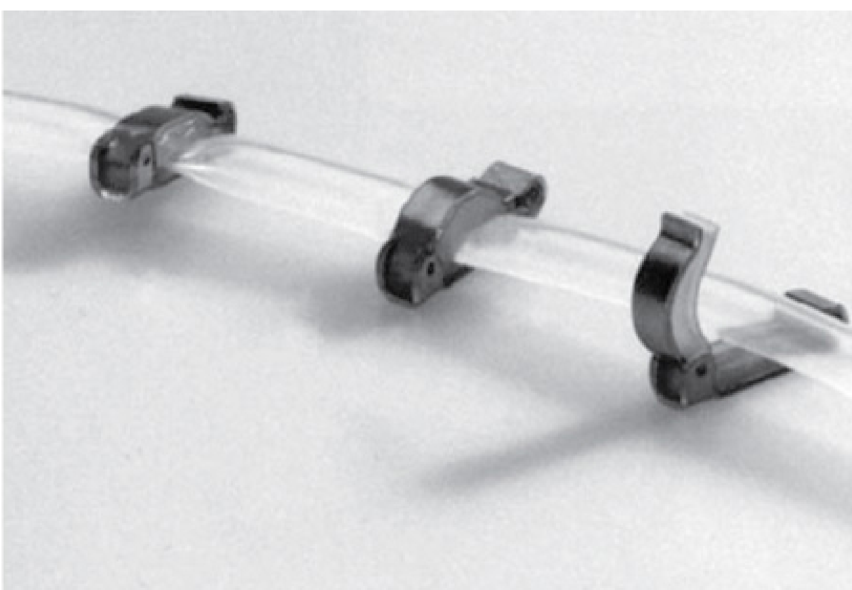
8. **Filshie Clip Application.** The titanium Filshie clip (Avalon Medical Corp, Williston, VT) is applied with the aid of a customized metal applicator that closes and locks the rim of the shorter upper jaw under the lip of the lower jaw (Fig. 41-29.5).

FIGURE 41-29.5



A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

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Filshie clip **A.** Single clip open. **B.** Closed clips around plastic tubing. (From Penfeld, 2000, with permission).

9. **Applicator Insertion.** At the beginning of clip application, a Filshie clip is held within its applicator and inserted through the laparoscopic cannula into the abdomen. A surgeon half closes the applicator's upper jaw to insert it and the clip through the laparoscopic cannula. Care must be taken not to grip the handle of the applicator too tightly because this may close and lock the clip prematurely (Penfield, 2000).

   Once the Filshie clip emerges through the cannula, the applicator is opened slowly. The jaw of the applicator has the potential to open quickly. This can result in the clip falling off the applicator and into the abdomen.

10. **Filshie Clip Placement.** After the clip is completely open, the clip and applicator are positioned with one jaw above and one below the tube. The entire width of the tube should lie across the base of the clip, and the distal hooked end of the lower jaw should be visible through the mesosalpinx.

11. **Filshie Clip Application.** Once satisfied that the clip is positioned correctly, the surgeon slowly squeezes the finger bar-spring handle to its full limit, back toward the handle backstop. With this action, the upper jaw of the clip is compressed slowly and locked under the hooked end of the lower jaw. This flattens the tube within the clip. The clip is released automatically from the applicator and locked onto the tube. These steps are repeated on the opposite fallopian tube. If there is any doubt about the clip placement, a second clip is applied correctly.

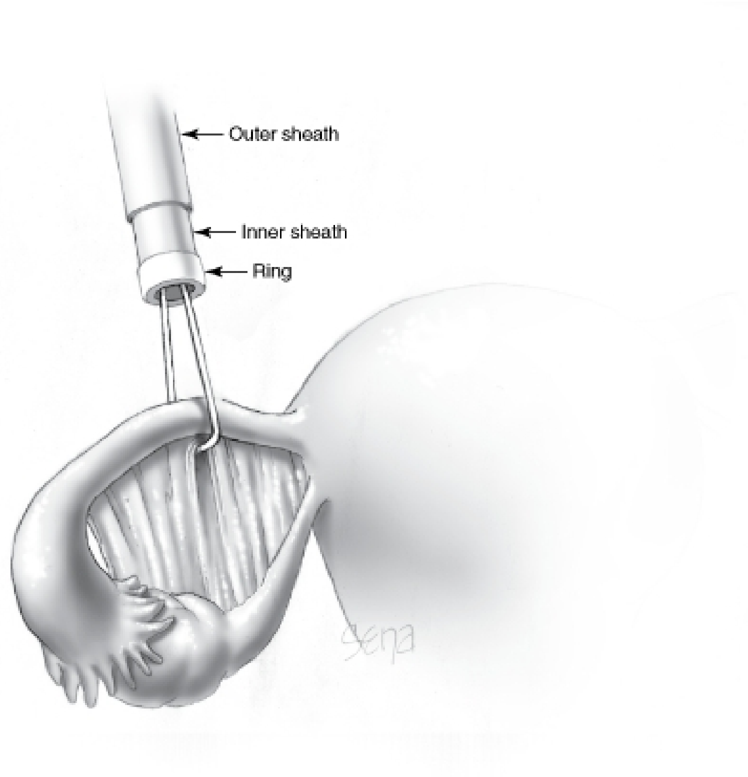
    Rarely, a fallopian tube may be transected by the clip. This usually is associated with a large fallopian tube that has been clipped too quickly. For completion, a clip is applied to both ends of the transected tube.

12. **Falope Ring (Silastic Band).** A Silastic Falope ring (ACMI, Southborough, MA) is applied with the aid of a customized metal applicator. In overview, applicator tongs draw a portion of tube up into an inner sheath, and an outer sheath then pushes a Silastic band off the inner sheath and onto the base of a loop of tube.

13. **Ring Loading.** Prior to its insertion into the abdomen, a Falope ring is stretched around the distal tip of the inner applicator sheath by means of a special ring loader and ring guide.

14. **Ring Placement.** Once inserted into the abdomen, the applicator's tongs are placed completely around the fallopian tube approximately 3 cm from the cornua, and they grasp the mesosalpinx directly at its attachment to the tube. This prevents excess mesosalpinx from being drawn into the inner sheath (Fig. 41-29.6).

FIGURE 41-29.6

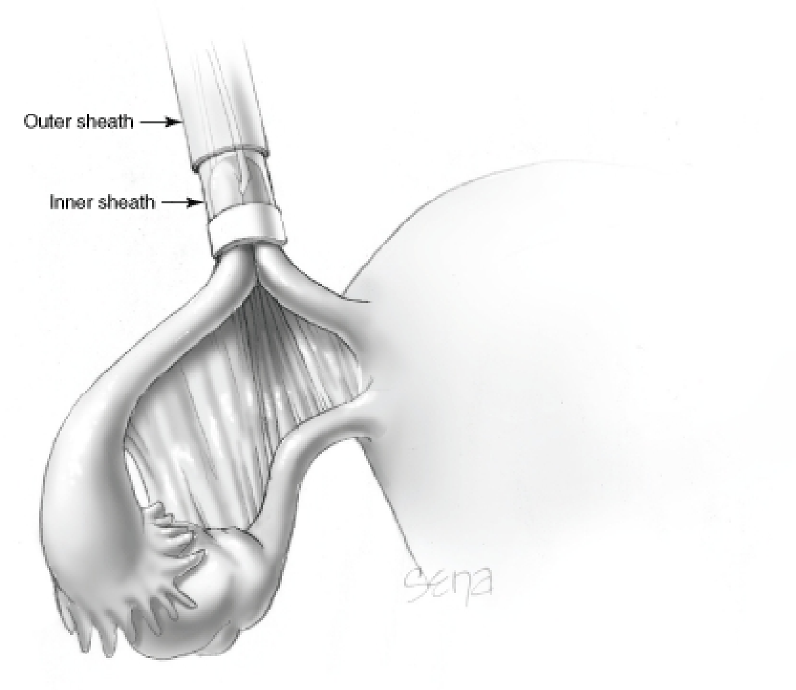


Falope ring applicator placement.

15. **Ring Application.** A trigger on the applicator retracts the tongs and draws a knuckle of tube approximately 1.5 cm into the inner sheath. The total length of tube contained within the inner sheath is 3 cm (Fig. 41-29.7).

    The outer sheath then is advanced toward the knuckle of the tube. This pushes the Silastic band off the inner sheath and onto the knuckle base (Fig. 41-29.8). The loop of tube will blanch from ischemia following band placement. These steps are repeated on the opposite fallopian tube.

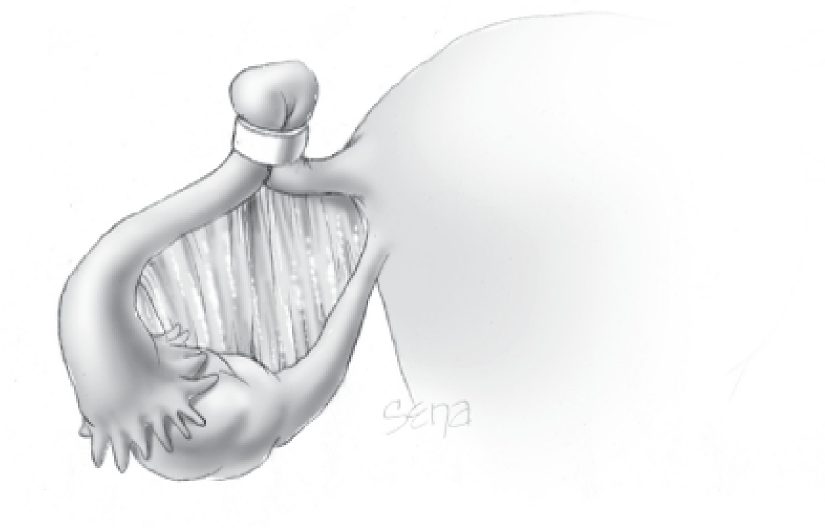
FIGURE 41-29.7



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Tube drawn into inner sheath.

FIGURE 41-29.8



Falope ring in place.

16. **Special Circumstances.** Tubal transection is uncommon, and a Falope ring can be applied to each of the divided segments. Vessels of the mesosalpinx can tear and bleed occasionally as the tongs and tube are drawn into the inner sheath. The Silastic band, once applied to the knuckle of the tube, will control bleeding in most instances, and use of electrosurgical coagulation to achieve hemostasis is needed infrequently.

17. **Pomeroy with Endoscopic Loop.** This procedure can be used as a sterilization technique but also has been used to excise fallopian tube ectopic pregnancies. A description and figures can be found in Section 41-30, Laparoscopic Salpingectomy.

Postoperative

Postoperatively, patients are given instructions similar to those following diagnostic laparoscopy.

41-30 LAPAROSCOPIC SALPINGECTOMY

For most women, laparoscopic management of ectopic pregnancy is the preferred approach. For some, laparoscopic salpingostomy is desired to preserve future fertility. In other cases, tubal rupture and damage or bleeding may not permit fallopian tube salvage. In these instances, laparoscopic salpingectomy is indicated.

In addition, salpingectomy also may be used to remove hydrosalpinges in women undergoing in vitro fertilization (IVF). Studies have shown improved pregnancy rates if such tubes have been excised (see Chap. 9, Hydrosalpinx). Less commonly, total salpingectomy can be used as a method of sterilization.

Preoperative

CONSENT

In addition to risks associated in general with laparoscopy, risks include conversion from a laparoscopic approach to laparotomy for procedure completion and injury to the ipsilateral ovary. Accordingly, the potential for oophorectomy should be discussed.

PATIENT PREPARATION

Because the risk of infection is low with both salpingectomy and laparoscopy, preoperative antibiotics typically are not required.

Intraoperative

Surgical Steps

1. **Anesthesia and Patient Positioning.** The patient is prepared and positioned for laparoscopic surgery.

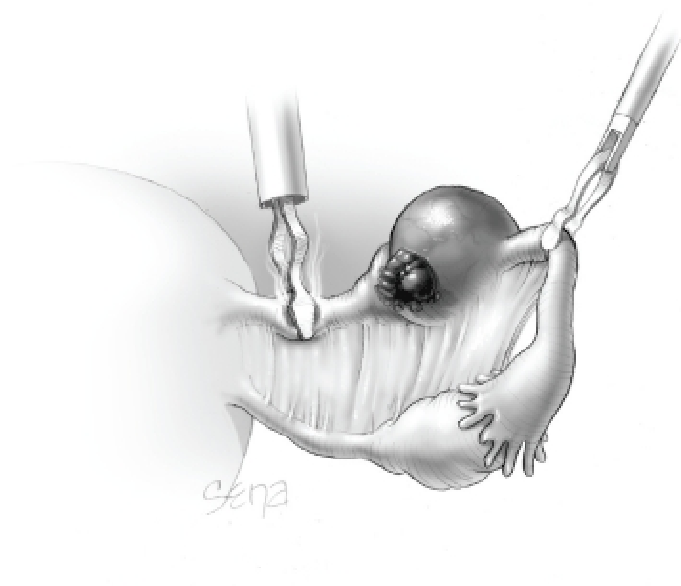
2. **Abdominal Entry.** The abdomen is entered laparoscopically, and typically two or three secondary accessory trocar sites are used (see Section 41-28, Laparoscopy). Depending on the size of the ectopic, at least one 10-mm or larger accessory trocar may be necessary to allow specimen removal at surgery's end.

3. **Mesosalpingeal Incision.** The fallopian tube is lifted and held with an atraumatic grasping forceps. Kleppinger bipolar electrode forceps are placed across a proximal portion of the fallopian tube. A cutting current at 25 W should suffice (Fig. 41-30.1). When 0 amperage of flow is noted, scissors then can be used to cut the desiccated, blanched tube (Fig. 41-30.2).

   The Kleppinger forceps are next advanced across the proximal mesosalpinx. Similarly, current is applied, and the desiccated tissue is cut. This process moves serially from the proximal mesosalpinx to its distal extent under the tubal ampulla.

   Alternatively, the scissors themselves may be attached to current. In this technique, vessels within the mesosalpinx first are coagulated electrosurgically and then are cut. As the distal mesosalpinx is cut, the tube is freed.

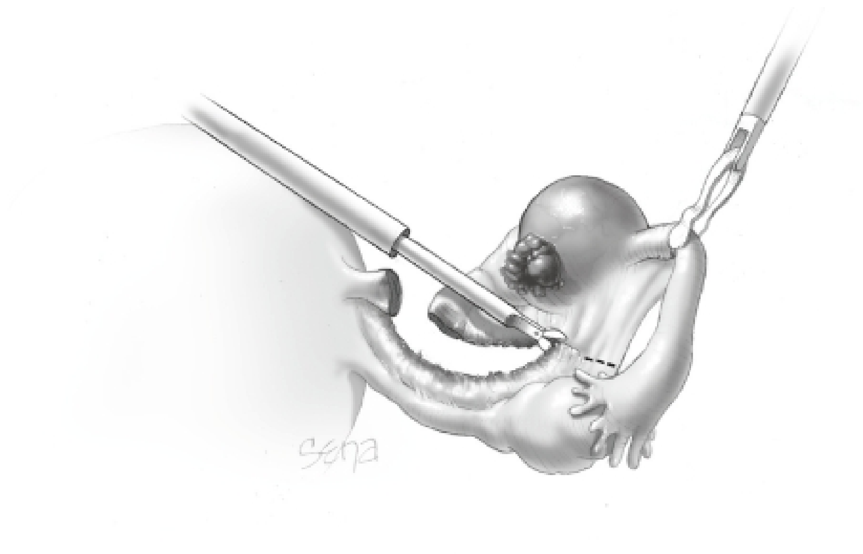
FIGURE 41-30.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Fallopian tube desiccation.

FIGURE 41-30.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

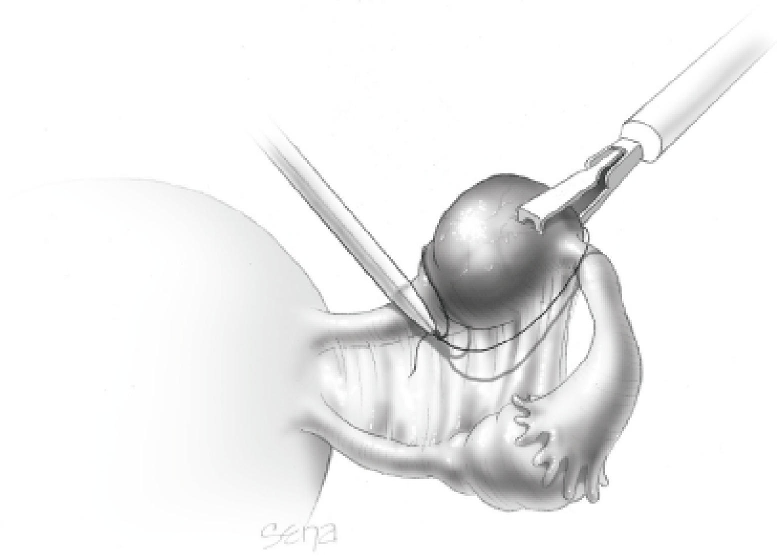
Mesosalpinx incision.

4. **Endoscopic Loop Ligation.** Alternatively, the vascular supply to the fallopian tube within the mesosalpinx can be ligated. Figure 41-30.3 shows an endoscopic suture loop encircling a knuckle of fallopian tube that contains the ectopic pregnancy. Two or three suture loops are placed sequentially, and the interposed portion of tube then is cut free with scissors (Fig. 41-30.4).

   Most tubal ectopic pregnancies are small and pliant. Accordingly, they can be held firmly by grasping forceps and drawn up into one of the accessory-site cannulas. The cannula, grasping forceps, and ectopic tissue then can be removed together.

   Larger tubal ectopic pregnancies may be placed in an endoscopic sac to prevent fragmentation as they are removed through the laparoscopic trocar sites (see Fig. 41-28.8). Alternatively, larger ectopic pregnancies can be divided with scissors or a laparoscopic morcellator and the smaller fragments removed.

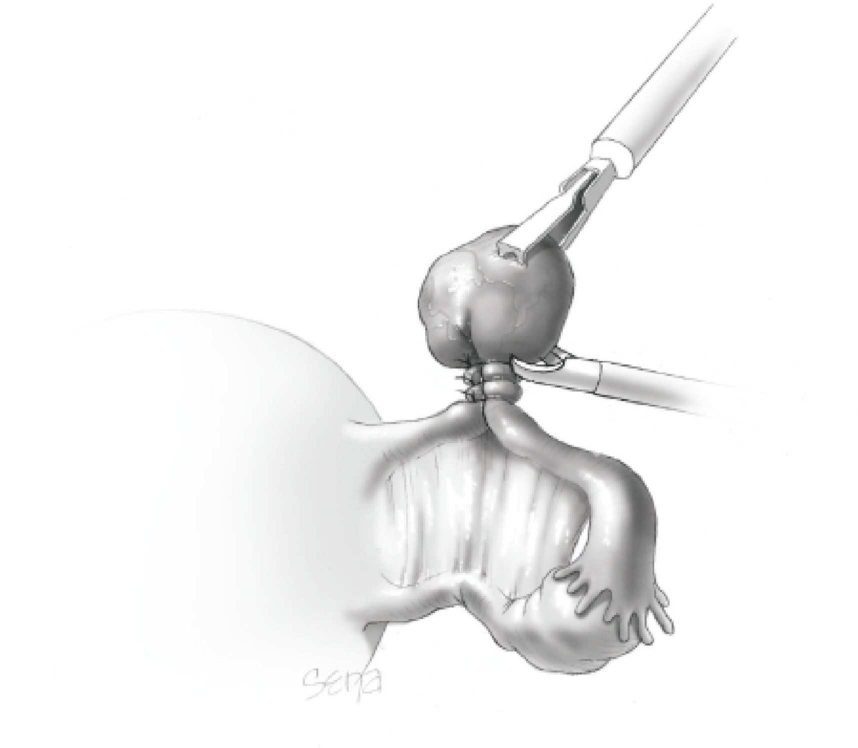
FIGURE 41-30.3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Endoscopic loop ligation.

FIGURE 41-30.4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Partial salpingectomy.

5. **Irrigation.** To prevent persistent trophoblastic tissue, the pelvis and abdomen should be irrigated and suctioned free of blood and tissue debris.

6. **Wound Closure.** Subsequent surgery completion steps should follow those of laparoscopy (see Section 41-28, Laparoscopy).

Postoperative

Guidelines for postoperative care mirror those of laparoscopic salpingostomy and can be found in Section 41-31, Laparoscopic Salpingostomy.

41-31 LAPAROSCOPIC SALPINGOSTOMY

For patients with ectopic pregnancy, laparoscopic salpingostomy offers the surgical advantages of laparoscopy and the opportunity to preserve fertility (see Chap 7, Salpingostomy). Accordingly, it should be considered one of the first-line treatments for those with ectopic pregnancies.

Preoperative

CONSENT

As noted earlier, treatment goals for ectopic pregnancy surgery include minimizing the effects of surgery, preventing persistent trophoblastic tissue, and preserving fertility in those so desiring it (see Section 41-25, Salpingectomy and Salpingostomy).

Surgical Approach

Laparoscopy offers patients significant advantages over laparotomy, including improved recovery and lower postoperative pain. The risks of this surgical approach are outlined in Section 41-28, Laparoscopy and should be included on any consent.

Bleeding

Because of the extreme vascularity of trophoblastic tissues, disruption of their vessels during removal of an ectopic pregnancy can lead to severe hemorrhage. The contractility of the tubal muscularis is minimal, and bleeding during salpingostomy must be controlled with external modalities such as electrosurgical coagulation. At times, bleeding may be extensive and persistent and necessitate salpingectomy. Prior to surgery, patients should be aware of this potential.

In an effort to improve hemostasis, vasoconstrictive agents such as vasopressin have been evaluated. Investigators describe diluting 20 IU of vasopressin in 20 to 50 mL of saline (Pouly, 1986; Ugur, 1996). The mesosalpinx then is infiltrated with approximately 10 mL of solution. Because of the potential systemic vasocontrictive effects of vasopressin, care must be taken to avoid intravascular injection. Additional complications and contraindications to its use are discussed in Section 41-18, Myomectomy. Benefits to vasopressin use include less frequent use of electrosurgery, shorter operating times, and lower conversion rates to laparotomy for surgery completion.

In an attempt to avoid the cardiovascular complications of vasopressin, Fedele and colleagues (1998) diluted 20 IU of oxytocin in 20 mL of saline and similarly injected the mesosalpinx. Oxytocin is purported to contract the smooth muscle fibers of the tube and cause vasoconstriction of mesosalpinx vessels. These researchers noted easier pregnancy enucleation, less bleeding, and less frequent use of electrosurgery.

Persistent Trophoblastic Tissue

During treatment of ectopic pregnancy, trophoblastic tissue can persist in as many as 3 to 20 percent of cases (see Chap. 7, Persistent Ectopic Pregnancy). Remnant implants typically involve the fallopian tube, but extratubal trophoblastic implants have been found on the omentum and on pelvic and abdominal peritoneal surfaces. Peritoneal implants typically measure 0.3 to 2.0 cm and appear as red-black nodules (Doss, 1998). Severe postoperative bleeding is the most serious complication of this persistent trophoblastic tissue (Giuliani, 1998).

The risk of persistent trophoblast tissue is highest following laparoscopic salpingostomy, especially in patients in whom small, early pregnancies are removed. In these pregnancies, a less well-defined cleavage plane between the interface of the invading trophoblast and the tubal implantation site develops. This may lead to a more difficult dissection and failure to completely removal all products of conception.

Preventive recommendations for this complication include irrigation and complete suctioning of the abdomen, limitation of the Trendelenburg position to limit blood and tissue flow to the upper abdomen, and use of endoscopic bags for removal of larger ectopic pregnancies (Ben-Arie, 2001).

Intraoperative

Surgical Steps

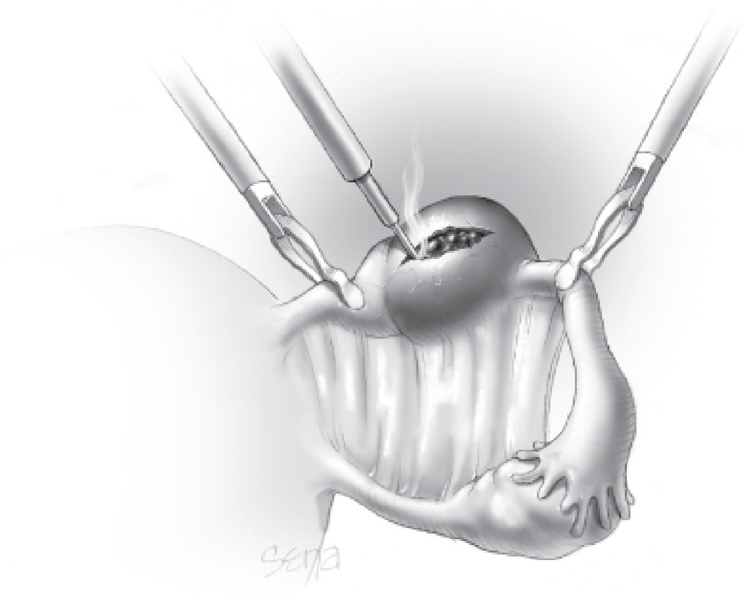
1. **Anesthesia and Patient Positioning.** The patient is prepared and positioned for laparoscopic surgery.

2. **Abdominal Entry.** The abdomen is entered laparoscopically, and typically two or three secondary accessory trocar sites are used (see Section 41-28, Laparoscopy). Depending on the size of the ectopic, at least one 10-mm or larger accessory trocar may be necessary to allow specimen removal at surgery's end.

3. **Salpingostomy.** The fallopian tube is lifted and held with atraumatic grasping forceps (Fig. 41-31.1). By means of a 22-gauge needle through one of the accessory trocar cannulas or separate abdominal insertion, a solution of vasopressin is injected into the mesosalpinx beneath the ectopic pregnancy.

   A unipolar needle tip electrode is set at a cutting voltage and used to create a 1- to 2-cm longitudinal incision. The incision should be positioned opposite the mesosalpinx and on the maximally distended portion of the tube that overlies the pregnancy. Laparoscopic scissors also may be used.

FIGURE 41-31.1

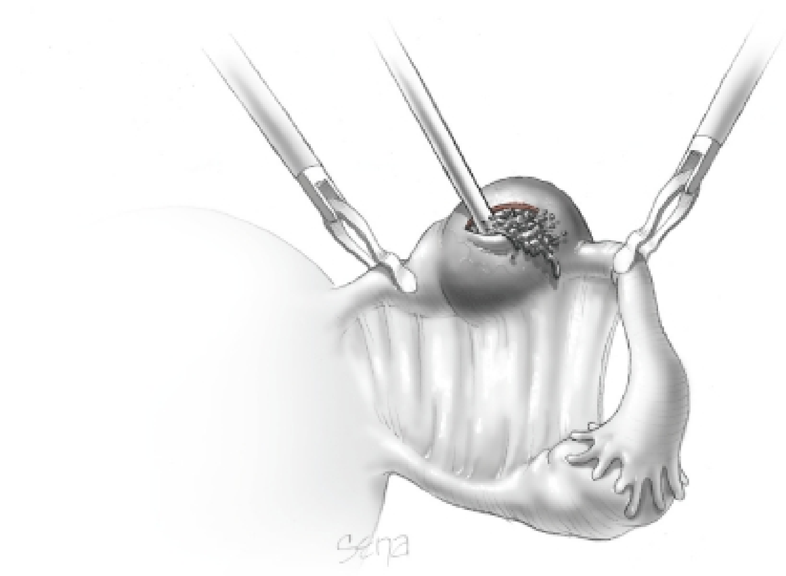


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Salpingostomy.

4. **Pregnancy Removal.** Atraumatic grasping forceps are used to hold one edge of the incision while a suction-irrigation probe tip is insinuated into the tissue plane between the tubal wall and ectopic pregnancy (Fig. 41-31.2). Hydrodissection is performed on one side of the tube and then the other. A combination of high-pressure hydrodissection and gentle blunt dissection with the suction irrigator is used to remove the entire product of conception from the tube. Alternatively, the pregnancy or its fragments may require extraction with the assistance of smooth grasping forceps.

FIGURE 41-31.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Hydrodissection.

5. **Hemostasis.** Bleeding points can be controlled with unipolar or bipolar electrosurgical coagulation. The tubal incision is left open to heal by secondary intention. Tulandi and Guralnick (1991) found no differences in subsequent fertility and adhesion formation between salpingostomy with or without tubal suturing.

6. **Specimen Extraction.** Most ectopic pregnancies are small and pliant. Accordingly, they can be held firmly by grasping forceps and drawn up into one of the accessory-site cannulas. The cannula, grasping forceps, and ectopic tissue then can be removed together.

   Larger ectopic pregnancies may be placed in an endoscopic sac to prevent fragmentation as they are removed through the laparoscopic trocar site (see Fig. 41-28.8).

7. **Irrigation.** To prevent persistent trophoblastic tissue postoperatively, the pelvis and abdomen should be irrigated and suctioned free of blood and tissue debris.

8. **Wound Closure.** Subsequent surgery completion steps should follow those of laparoscopy (see Section 41-28, Laparoscopy).

Postoperative

As with most laparoscopic surgeries, patients can resume preoperative diet and activity levels according to their comfort, typically within days. With end of any first-trimester pregnancy, the Rh status of the mother should be assessed. For Rh-negative patients, administration of 50 or 300 μg (1,500 IU) Rh_0 [D] immune globulin intramuscularly within 72 hours can minimize the risk of isoimmunization in future pregnancies.

To identify patients in whom trophoblastic tissue may persist, serial weekly serum β-hCG levels should be monitored (Seifer, 1997). Moreover, Spandorfer and associates (1997) compared serum β-hCG levels one day postoperatively with those drawn prior to surgery. They found a significantly lower percentage of persistent trophoblastic tissue if the β-hCG level fell more than 50 percent and no cases if the level declined by greater than 77 percent. During surveillance contraception should be used to avoid confusion between persistent trophoblastic tissue and a new pregnancy.

41-32 OVARIAN DRILLING

Ovarian drilling is a technique of puncturing the ovarian capsule with a laser beam or an electrosurgical needle using a laparoscopic approach. Similar to ovarian wedge resection, this procedure's end goal is to reduce the amount of androgen-producing tissue. Ovarian wedge resection, however, requires a laparotomy approach, and for best results, excision of one half to three fourths of the ovarian medulla (Halbe, 1972). As a result of the long capsular incision required for this degree of resection, infertility secondary to adhesions was found to complicate many postoperative courses (Buttram, 1975; Toaff, 1976). To minimize this risk and avoid the need for laparotomy, ovarian drilling techniques using laparoscopy were developed in the early 1980s.

Compared with medical management, ovarian drilling has lower rates of ovarian hyperstimulation syndrome (OHSS) and multifetal gestation. Disadvantages include the surgical risks of laparoscopy and the risk of pelvic adhesion formation (Donesky, 1995). For these reasons, ovarian drilling is viewed as a second-line therapy. It can be useful in patients who fail to ovulate with clomiphene citrate, are at risk for OHSS, or who desire to minimize their risk for multifetal gestation. An additional discussion of this procedure's advantages, disadvantages, and indications can be found in Chapter 20, Ovarian Drilling.

Preoperative

CONSENT

Relatively few complications arise immediately after ovarian drilling. Hemorrhage, infection, and thermal bowel injury are infrequent. Similarly, ovarian atrophy following drilling is rare but has been reported (Dabirashrafi, 1989).

Adhesion formation following this procedure, however, is common. Most of these adhesions at second-look laparoscopy typically have been graded as minimal or mild (GÃ¼rgan, 1991). Moreover, researchers have described only a minimal, if any, impact of these adhesions on fertility (GÃ¼rgan, 1992; Naether, 1993). The risk of infertility secondary to adhesive disease, however, should be discussed with the patient prior to surgery.

Intraoperative

INSTRUMENTS

Ovarian drilling has been described using monopolar or bipolar electrosurgery or using carbon dioxide, argon, or Nd-YAG laser. Currently, no studies support the superiority of one modality (Strowitzki, 2005).

NUMBER OF OVARIAN PUNCTURES

Punctures into the ovarian capsule typically are 2 to 4 mm wide and 4 to 10 mm deep. Although techniques using as many as few as 4 or as many as 40 punctures per ovary have been described, there are a few studies that have investigated the optimal number of punctures (Farquhar, 2004). For example, Malkawi and Qublan (2005) showed that 5 punctures per ovary compared with 10 resulted in equally improved pregnancy rates and similarly low rates of postprocedural OHSS and multifetal gestation.

Surgical Steps

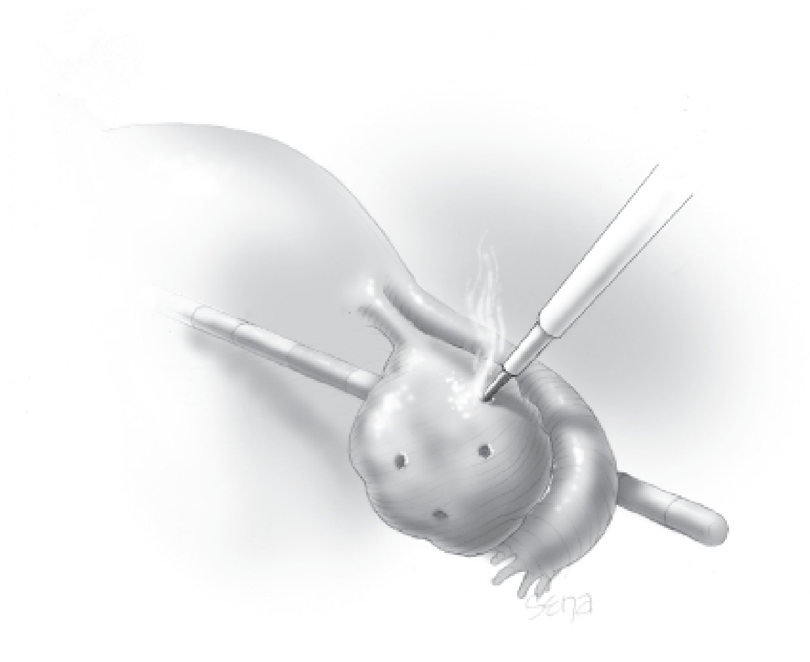
1. **Anesthesia and Patient Positioning.** Patient positioning and anesthesia mirror that for other laparoscopic procedures (see Section 41-28, Laparoscopy).

2. **Abdominal Entry.** Three incisions are used for this laparoscopic procedure. In addition to an infraumbilical incision, two bilateral lower abdominal incisions are made (see Fig. 41-28.1). These incisions serve as entry sites for the electrosurgical needle tip and blunt manipulating probe.

3. **Ovarian Drilling.** The ovary is elevated with a blunt probe. The electrosurgical current is set at 30 to 60 W cutting mode. An electrosurgical needle tip is used to puncture the ovary perpendicular to the capsular surface and to pierce the follicular cysts that are characteristic of PCOS. Three to five punctures are placed symmetrically on the anterior surface of the ovary (Fig. 41-32.1). Drilling is avoided on the lateral surfaces of the ovaries to minimize adhesions and is avoided at the ovarian hilus to limit bleeding risk. The needle is inserted to a depth of 4 to 10 mm. Electric current is applied for 3 to 4 seconds.

   The surface of the ovary can be irrigated with saline or lactated Ringer's solution to cool the capsular surface (Strowitski, 2005).

FIGURE 41-32.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Ovarian drilling.

4. **Adhesion Barriers.** Because of the risk for adhesion formation, some investigators have used adhesion barrier products following ovarian drilling. Greenblatt and Casper (1993), however, showed no improvement in adhesion prevention following this procedure using Interceed Adhesion Barrier (Ethicon, Summerville, NJ). No other studies have addressed the efficacy of other adhesion prevention products.

Postoperative

Postoperatively, patients are given instructions similar to those following diagnostic laparoscopy.

41-33 LAPAROSCOPIC OVARIAN CYSTECTOMY

Many studies have attested to the efficacy and safety of laparoscopic cystectomy for the management of ovarian cysts. Moreover, because of associated benefits, such as shorter hospital stay, quicker patient recovery, and lower rates of postoperative pain, infection, and adhesions, a laparoscopic technique is advocated by many as the preferred approach in women with ovarian cysts and a low risk of malignancy (see Chap. 9, Laparoscopy).

Preoperative

PATIENT EVALUATION

Sonography

Sonography is the primary tool used to diagnose ovarian pathology, and the sonographic characteristics of a cyst aid in determining preoperatively the malignant potential of a given lesion. In patients with indeterminate ovarian cysts following sonography, magnetic resonance (MR) imaging has been shown to enhance discrimination.

Tumor Markers

Serum cancer antigen 125 (CA125) levels typically are drawn preoperatively in postmenopausal patients and in any women whose tumor displays other risk factors for malignancy (see Chap. 9, Observation). Additionally, serum alpha-fetoprotein (AFP), lactate dehydrogenase (LDH), inhibin, and β-hCG levels may be measured to exclude other ovarian neoplasms (see Chap. 36, Laboratory Testing).

CONSENT

Prior to surgery, patients should be informed of the unique complications associated with laparoscopy. Specific to ovarian cystectomy, the risks of oophorectomy due to bleeding or extreme ovarian damage should be discussed. Obviously, because many cysts are removed because of concerns for potential malignancy, patients should be aware of the steps involved in the surgical staging of ovarian cancer.

PATIENT PREPARATION

Because of low rates of pelvic and wound infection follow ovarian cystectomy and laparoscopy, antibiotic prophylaxis typically is not required. Bowel preparation is not usually required but may be considered if extensive bowel adhesions are suspected.

Intraoperative

Surgical Steps

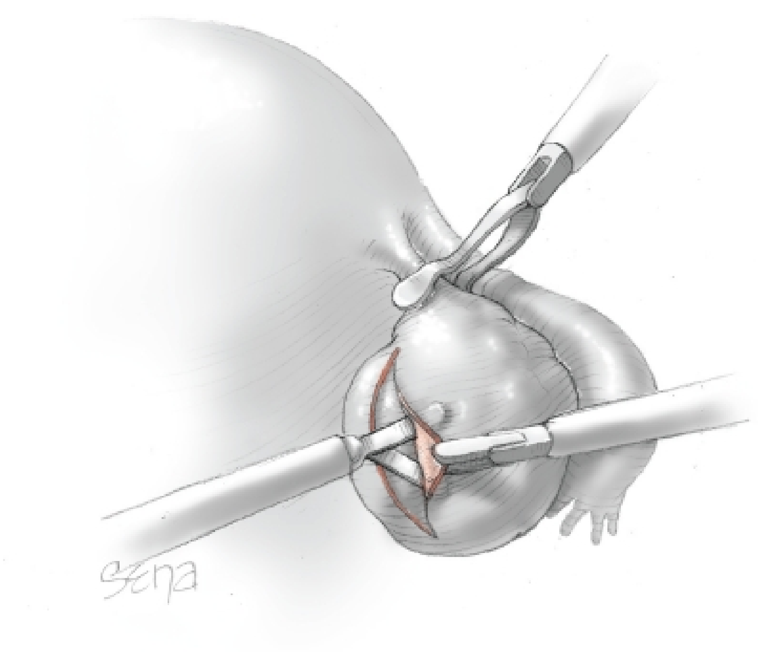
1. **Anesthesia and Patient Positioning.** As with most laparoscopic procedures, a patient should be placed in the dorsal lithotomy position after adequate general anesthesia has been delivered. In anticipation of possible hysterectomy as a part of ovarian cancer staging, the vagina and abdomen should be surgically prepared. A Foley catheter is placed to avoid operative field obstruction by or injury to a full bladder. The patient then is draped to allow sterile access to the vagina and abdomen.

2. **Abdominal Entry.** Primary and secondary trocar sites are placed as described in Section 41-28, Laparoscopy. Typically, two or three accessory trocar sites are required.

   Once the abdomen is entered, the pelvis and upper abdomen should be inspected for signs of malignancy, such as ascites and peritoneal implants. Cellular washings from these areas should be obtained and saved until frozen-section analysis of the specimen has excluded malignancy. Similarly, identified peritoneal implants should be biopsied and sent for frozen-section analysis.

3. **Ovarian Incision.** A blunt probe is place under the utero-ovarian ligament and posterior ovarian surface to elevate the ovary. An atraumatic grasping forceps then steadies the ovary, and the blunt probe is removed (Fig. 41-33.1). A unipolar needle tip electrode set at a cutting voltage is used to incise the ovarian capsule that overlies the cyst. Care is taken to avoid puncture of the cyst.

FIGURE 41-33.1



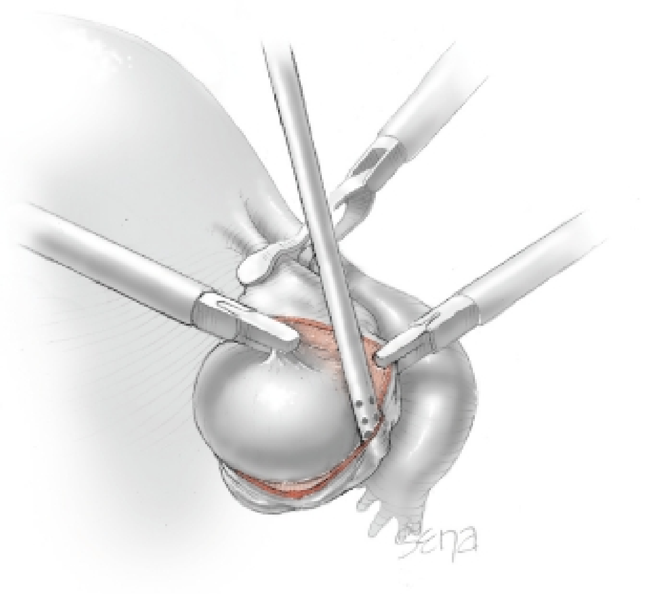
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Ovarian incision.

4. **Cyst Dissection.** A space between the ovary and cyst wall is created using blunt forceps or dissecting scissors (see Fig. 41-33.1). Atraumatic grasping forceps are used to hold one edge of the incision while a blunt probe or suction-irrigation probe tip is insinuated in the tissue plane between the ovarian capsule and cyst wall (Fig. 41-33.2).

   Blunt or hydrodissection is performed on one side of the cyst and then the other. Depending on the adherence of the cyst to its surrounding ovarian tissue, cystectomy at times may require sharp dissection with scissors. During dissection, points of bleeding may be coagulated, or isolated vessels may be grasped and coagulated.

FIGURE 41-33.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

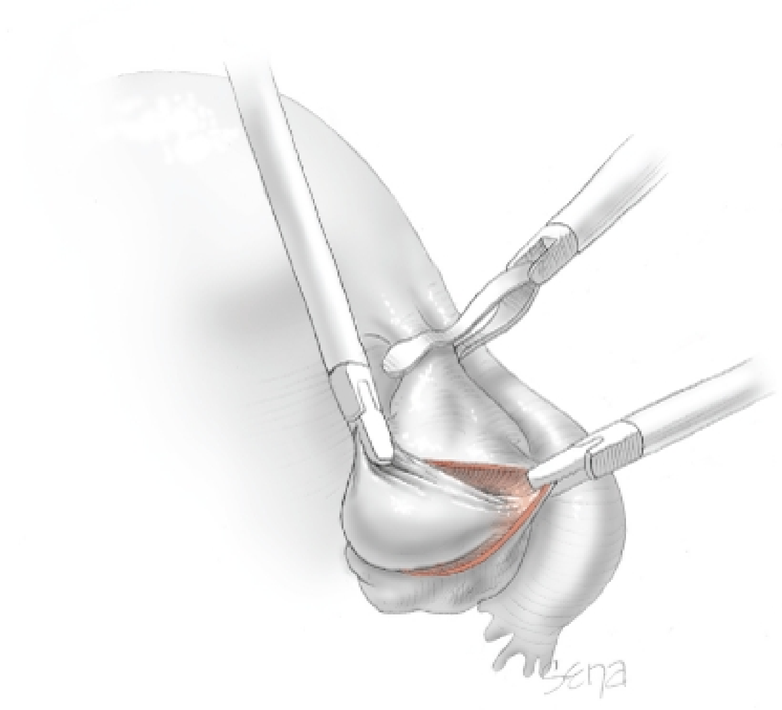
Cyst dissection.

5. **Cyst Removal.** Following enucleation from the ovary, the cyst is placed into an endoscopic bag (see Fig. 41-28.8). The opening of the sac is closed and brought up to the anterior abdominal wall. Depending on its size, the cyst and endoscopic bag may be removed in toto through one of the secondary accessory trocar sites. In this setting, the laparoscopic cannula is removed first, followed by the cyst contained within the sac.

   Alternatively, with larger cysts, the cannula is removed, and the entire pursed opening of the bag is drawn up through the trocar incision and fanned out onto the skin surface. The open edges of the bag are pulled upward to lift and press the cyst up against the incision. A needle tip then is directed into the sac and pierces the cyst. An attached syringe is used to aspirate the contents. Any stray fluid is retained by the endoscopic sac. The endoscopic sac and decompressed cyst wall then are removed together through the incision.

6. **Cyst Rupture.** Not uncommonly during the dissection of the cyst away from the ovary, the cyst will rupture. The cyst wall then is removed using a "stripping" technique (Fig. 41-33.3). The edge of the ovarian capsule is held with grasping forceps while the collapsed cyst is grasped with a second pair. The grasping forceps then strip the cyst wall away from the underlying ovarian stroma (Mahdavi, 2004). Histologically, Muzii and colleagues (2002) showed that this technique in nonendometriotic lesions spared ovarian tissue and did not strip away normal ovarian tissue and follicles.

FIGURE 41-33.3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Cyst wall removal.

7. **Ovary Closure.** Because of increased difficulty and time associated with laparoscopic suturing, the ovarian capsule is not sutured closed following cyst removal. Several studies have shown that leaving the capsule open does not lead to increased adhesion formation (Marana, 1991; Wiskind, 1991).

8. **Wound Closure.** The specimen is submitted in most cases for immediate frozen-section analysis. If benign findings are noted, then steps toward surgical closure begin. If malignancy is found, then surgical staging via laparotomy should ensue (see Chap. 35, Surgical Staging).

   The finishing laparoscopic steps are found in Section 41-28, Laparoscopy.

Postoperative

Following laparoscopic ovarian cystectomy, instructions similar to those for general laparoscopy are given.

41-34 LAPAROSCOPIC SALPINGO-OOPHORECTOMY

Laparoscopy can be used to safely remove many adnexa and in most cases offers a faster recovery and less postoperative pain than laparotomy. As discussed in Chapter 9, Laparoscopy, indications for adnexectomy vary but may include torsion, ovarian cyst rupture, suspicion of ovarian malignancy, and symptomatic ovarian remnant. In addition, prophylactic oophorectomy is considered often in women with or at risk for cancers involving the breast, ovary, and colon (see Chap. 35, Prophylactic Surgery). However, there are clinical settings in which laparotomy is indicated, such as when the suspicion of cancer is high, extensive pelvic adhesions are anticipated, and ovarian masses are large.

Preoperative

PATIENT EVALUATION

Salpingo-oophorectomy typically is performed to remove ovarian pathology, and sonography is the primary tool used for diagnosis. In patients in whom anatomy may be unclear, magnetic resonance (MR) imaging may add additional information. As discussed in Chapters 35, Imaging and 36, tumor markers may be drawn prior to surgery if malignancy is suspected.

CONSENT

Prior to surgery, patients should be informed of the unique complications associated with laparoscopy. Specific to salpingo-oophorectomy, the risk of ureteral injury should be discussed. Obviously, because many adnexa are removed due to concerns of potential malignancy, patients should be familiar with the steps involved in the surgical staging of ovarian cancer (see Chap. 35, Surgical Staging).

PATIENT PREPARATION

Unless an ovarian abscess is identified, antibiotic prophylaxis is generally not required and is administered according to the preference of the surgeon.

Intraoperative

Surgical Steps

1. **Anesthesia and Patient Positioning.** As with most laparoscopic procedures, the patient should be placed in the dorsal lithotomy position after adequate general anesthesia has been delivered. Because of possible hysterectomy as a part of ovarian cancer staging, the vagina and abdomen are surgically prepared, and a Foley catheter is placed.

2. **Trocar and Laparoscope Insertion.** Primary and secondary trocar sites are placed as described in Section 41-28, Laparoscopy. Typically, two or three accessory trocar sites are required.

3. **Pelvic Inspection and Washings.** Once abdominal access has been completed, the pelvis and upper abdomen should be inspected for signs of malignancy. Cell washings from these areas can be obtained using a laparoscopic suction-irrigating tool and should be saved until frozen-section analysis of the specimen has excluded malignancy. Similarly, identified suspicious peritoneal implants are biopsied and sent for frozen-section analysis. If adhesions are present, they are lysed to restore normal anatomy for the procedure.

4. **Ureter Location.** The ureter lies close to the infundibulopelvic (IP) ligament, and its course should be noted. If the location of the ureter is not clear, the peritoneum lateral to the ureter is incised (Fig. 41-34.1) The medial peritoneal leaf of the broad ligament is elevated and placed on traction. If the ureter is not immediately seen, then a blunt probe or suction tip is used in a sweeping motion from top to bottom along the medial peritoneal leaf to identify the ureter.

FIGURE 41-34.1

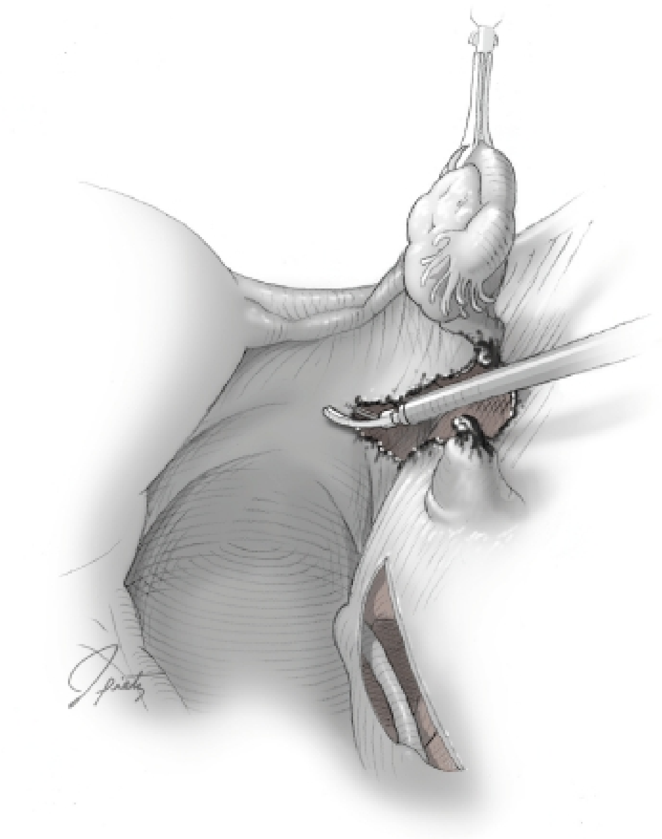
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Infundibulopelvic ligament coagulation.

5. **Infundibulopelvic Ligament Coagu-lation.** Ligation of the ovarian vessels within the IP ligament can be completed with endoscopic loop ligatures, electrosurgical coagulating devices, harmonic scalpel, or stapler depending on the preference of the surgeon Fig. 41-34.1. Once these vessels are occluded, the IP is severed proximally.

6. **Opening of the broad ligament.** After transection of the IP, incision of the broad ligament's posterior leaf is extended medially (Fig. 41-34.2).

FIGURE 41-34.2

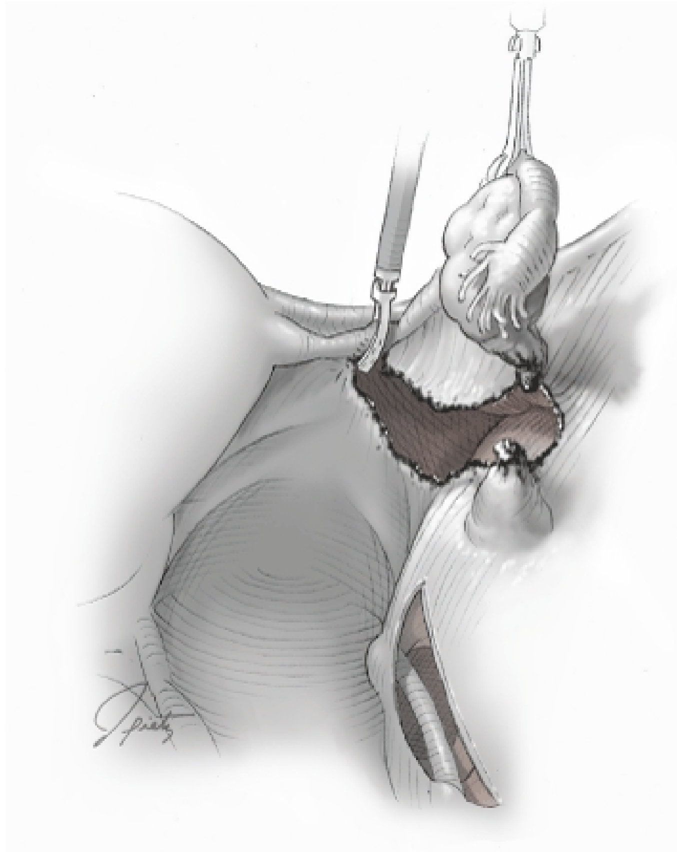


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Opening of the broad ligament.

7. **Utero-ovarian Ligament Coagulation.** The utero-ovarian ligament, proximal fallopian tube, and round ligament are identified posterior to the round ligament. Similarly to the IP, these may be coagulated, stapled, or ligated (Fig. 41-34.3). Distal to this occlusion, the utero-ovarian ligament and fallopian tube are transected, and the adnexa is freed.

FIGURE 41-34.3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Fallopian tube and utero-ovarian ligament coagulation.

8. **Adnexa Removal.** A number of endoscopic bags are available for tissue removal (see Fig. 41-28.8). The specimen is dropped into the sac, which is closed and brought up to the anterior abdominal wall. Depending on its size, the adnexa and endoscopic bag may be removed in toto through one of the secondary accessory trocar sites. In this setting, the laparoscopic cannula is removed first, followed by the specimen contained within the sac.

   Alternatively, with larger cystic ovaries, the cannula is removed, and the entire pursed opening of the bag is drawn up through the trocar incision and fanned out onto the skin surface. The open edges of the bag are pulled upward to lift and press the ovary against the incision. A needle tip is directed into the trocar incision. The ovary is pierced, and aspiration drainage is completed by an attached syringe. Any stray fluid is retained by the endoscopic sac. The sac and decompressed adnexa then are removed together through the incision.

9. **Wound Closure.** If malignancy is suspected, the specimen is submitted for immediate frozen-section analysis. If benign findings are noted, then steps toward surgical closure begin as indicated in Section 41-28, Laparoscopy. If malignancy is found, then surgical staging via laparotomy should ensue.

Postoperative

Advantages to laparoscopy include a rapid return to normal diet and activities and postoperative complication rates are low. If both

adnexa are removed, then hormone-replacement therapy is considered in appropriate candidates (see Chap. 22, Current Approach to Hormone Replacement Administration).

41-35 HYSTEROSCOPY

Hysteroscopy allows an endoscopic view of the endometrial cavity and tubal ostia for both the diagnosis and operative treatment of intrauterine pathology. During the last two decades, the role of hysteroscopy in modern gynecology has expanded rapidly with development of more effective hysteroscopic instruments and smaller endoscopes.

Indications for hysteroscopy vary and include evaluation and in some cases, treatment of infertility, recurrent miscarriage, abnormal uterine bleeding, amenorrhea, and retained foreign bodies. With hysteroscopic techniques, abnormal bleeding can be treated with endometrial ablation, polypectomy, or submucous myomectomy. Infertility may be improved with incision of intrauterine adhesions or septa. Additionally, obstructed tubal ostia may be unblocked or dilated. Alternatively, for those seeking sterilization, tubal occlusion devices can serve as an effective and safe method of contraception.

Preoperative

PATIENT EVALUATION

Because the indications for hysteroscopy are varied, patient evaluations for specific disorders are discussed in their respective chapters. However, pregnancy is an absolute contraindication to hysteroscopy and should be excluded with serum or urine β-hCG testing prior to surgery. In addition, cervicitis or pelvic infection should be treated prior to hysteroscopy, and screening for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* is warranted in those with risk factors (see Chap. 1, Ovarian Cancer). For those with abnormal bleeding and significant risks for endometrial cancer, preoperative endometrial pipelle sampling is reasonable because seeding of the peritoneal cavity with cancer cells has been noted following hysteroscopy.

If diagnostic hysteroscopy is planned to locate and remove a foreign body, preoperative imaging, usually with transvaginal sonography, is recommended. For example, in some cases, an intrauterine device (IUD) or retained fetal bone may have perforated the uterine wall, lie predominantly outside the uterus, and thus be best removed by laparoscopy.

CONSENT

The risk of complications for women undergoing hysteroscopy is low and is cited at less than 1 to 3 percent (Hulka, 1993; Jansen, 2000; Propst, 2000). Complications are similar to those associated with dilatation and curettage and include uterine perforation, inability to sufficiently dilate the cervix, hemorrhage, cervical laceration, and postoperative endometritis. In addition, because either gas or liquid medium is required to distend the endometrial cavity during hysteroscopy, gas venous embolism and excessive intravascular fluid absorption are risks, as discussed later. In general, the risk of complication increases with the length and complexity of the procedure planned.

In the event of uterine perforation during hysteroscopy, diagnostic laparoscopy often is warranted for evaluation of the surrounding pelvic organs. Thus, patients should be additionally consented and aware of the possible need for laparoscopy.

PATIENT PREPARATION

Endometrial Thickness

In premenopausal women, hysteroscopy ideally is performed in the early proliferative phase of the menstrual cycle, when the endometrium is relatively thin. This allows small masses to be identified and removed easily. Alternatively, agents that induce endometrial atrophy such as progestins, combination oral contraceptives, danazol, and gonadotropin-releasing hormone (GnRH) agonists have been administered individually prior to anticipated surgery. Although these effectively thin the endometrium, many of these agents have disadvantages, including expense, adverse side effects, and surgical delay while atrophy ensues.

Cervical Dilatation

For operative hysteroscopy, dilatation of the cervix typically is required to insert an 8- to 10-mm hysteroscope or resectoscope. To minimize the risk of bleeding that may obscure the operative view and to lower the risk of uterine perforation, laminaria tents may be placed the day before surgery, as described in Section 41-16, Sharp Dilatation and Curettage. Alternatively, 100 μg misoprostol

(Cytotec, Pfizer, New York, NY), a synthetic prostaglandin E_1 analogue, may be administered orally the night before and again the morning of surgery to aid cervical softening.

Intraoperative

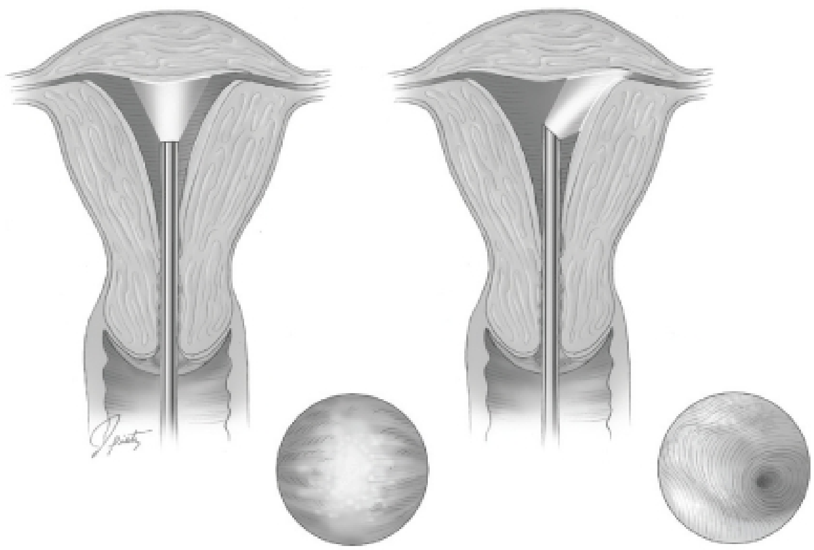
INSTRUMENTS

Hysteroscopy requires a hysteroscope, light source, uterine distention medium, and in many cases a video camera system.

Rigid Hysteroscope

Most hysteroscopes consists of an optical telescope with a diameter of 3 to 4 mm surrounded by an outer sheath. Individual endoscopes offers specific angles of view, and although 0- through 30-degree angles are available, 0- or 12-degree hysteroscopes allow the easiest orientation within the uterine cavity for most procedures (Fig. 41-35.1).

FIGURE 41-35.1

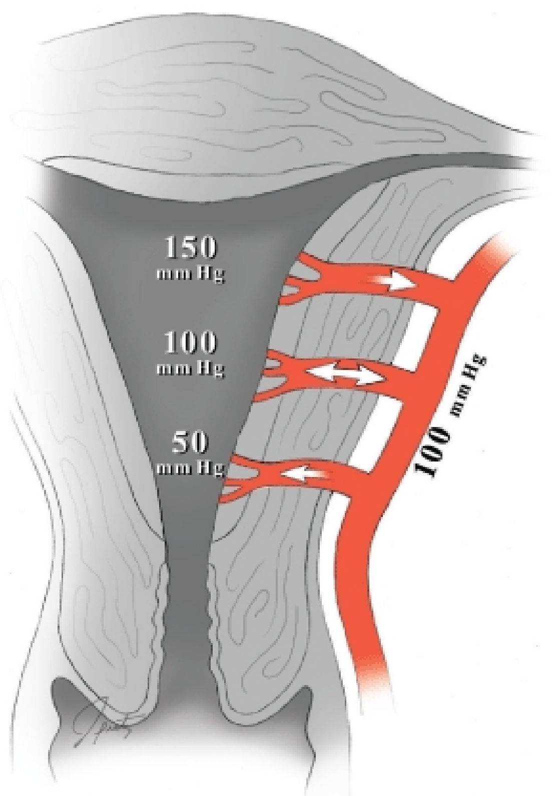


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Hysteroscopic views.

The outer sheath also offers variable features. It may be constructed to allow either unidirectional or continuous flow of distending media and may contain one, two, or no operative ports for instruments. Sheaths that allow continuous flow, that is, inflow and outflow circulation of the distention medium, are most valuable in patients in whom bleeding or large fluid volume deficits are a potential (Fig. 41-35.2). This circulation helps to clear blood from the operative field and assists with fluid volume deficit calculation. Volume deficits are calculated by the amount of distending media delivered subtracted by the amount returned through collection.

FIGURE 41-35.2



Distention medium flow varies depending on intrauterine pressure.

Resectoscope

If resection of intrauterine tissues is planned, then a resectoscope may be used. This tool consists of inner and outer sheaths. The inner sheath houses a 3- to 4-mm telescope and a channel for fluid medium inflow, whereas the 8- to 10-mm outer sheath allows fluid egress from the uterus through a series of small holes near the sheath's distal end. By means of a spring mechanism, the resection loop can be extended and then retracted to shave off contacted tissues.

Flexible Hysteroscope

Flexible hysteroscopes are available that have tips that can deflect over a range of 120 to 160 degrees. Although their optical view is less clear than that with rigid hysteroscopes, they offer surgeons the ease of maneuvering within irregularly shaped endometrial cavities.

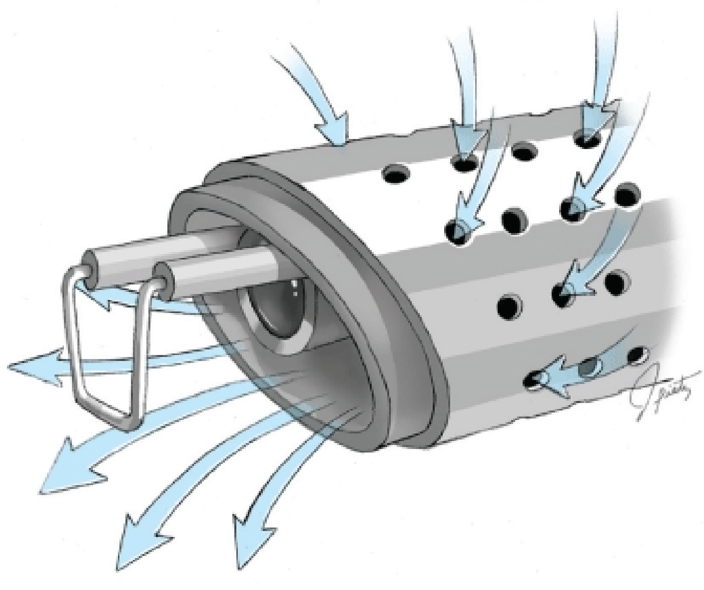
Distention Media

Because the anterior and posterior uterine walls lie in apposition, a distention medium is required to expand the endometrial cavity for viewing. Media include carbon dioxide (CO_2), saline, and low-viscous fluids such as sorbitol, mannitol, and glycine solutions (Table 41-35.1). Each group has distinct advantages and properties. To expand the cavity, intrauterine pressures of these media must reach 45 to 80 mm Hg (Tulandi, 1999). Rarely is more than 100 mm Hg required. Moreover, because for most women mean arterial pressure approximates 100 mm Hg, higher pressures can result in increased intravasation of medium into the patient's circulation and fluid volume overload (Fig. 41-35.3).

Table 41-35.1 Osmolality and Sodium Concentration of Hysteroscopic Distention Media		
Medium	**Osmolality, (mOsm/kg H_2O)**	**Sodium Concentration,(mEq/L)**
Serum	290	135â€"145
Glycine 1.5%	200	â€"
Sorbitol 3% + mannitol 0.5%	178	â€"
Mannitol 5%	280	â€"
0.9% Saline	308	154
Ringer's lactate	273	130

From Cooper, 2000, with permission.

FIGURE 41-35.3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Distention medium flow through resectoscope.

Carbon Dioxide

This commonly used distention medium, when used under pressure, tends to flatten the endometrium and gives excellent visibility. A continuous flow is necessary to replace any gas lost through the tubes, and typically flow rates of 40 to 50 mL/min are adequate.

Rates higher than 100 mL/min are associated with increased risks for gas embolism and therefore are discouraged. Specialized hysteroscopic insufflating machines that limit maximum flow rates should be used. Importantly, because laparoscopic insufflating machines can permit flow rates over 1,000 mL/min, these should never be used for hysteroscopy.

Disadvantages to CO_2 include its tendency, when mixed with blood or mucus, to form visually obstructive gas bubbles. Accordingly, prior to hysteroscope insertion, blood and mucus should be carefully removed from the cervical os with a dry swab (Sutton, 2006). Similarly, use of CO_2 with thermal energy sources is avoided because smoke production prohibits adequate visualization. Because of these limitations, CO_2 is best used in patients in whom minimal bleeding is anticipated, such as those needing diagnostic hysteroscopy or requiring simple operative excision (Bieber, 2003).

The most serious complication associated with CO_2 use is venous gas embolism. If vessels are opened during cervical dilation or endometrial disruption, gas under pressure can be forced into the vasculature, and any undissolved portion can reach the lungs. However, because CO_2 is many times more soluble in plasma than room air, it typically dissolves sufficiently during transit from the pelvic region (Corson, 1988). As a result, pulmonary embolism is rare, and severe embolism complicated only 0.03 percent of nearly 4,000 diagnostic CO_2 hysteroscopies in a review of cases by Bradner and colleagues (1999). Avoidance of a steep Trendelenburg position, which lowers the chest to a level below pelvic vessels, is recommended to reduce the risk of pulmonary embolism (Brooks, 1997).

Fluid Media

Bleeding is common with operative hysteroscopy procedures, and fluid media typically are selected in these cases because of their optical clarity and ability to mix with blood.

The main risk of fluid distention media, however, involves increased fluid absorption and fluid volume overload. Volume overload may develop with any of the fluid media and results from a variety of mechanisms. For example, absorption across the endometrium, intravasation through surgically opened venous channels, and spill from the fallopian tubes with absorption by the peritoneum all have been suggested. Accordingly, clinical settings in which procedures are long, increased distention pressure is used, large tissue areas are resected, or a more vascular endothelium is present, all carry a greater risk.

Saline, lactated Ringer's solution, and 5-percent mannitol are isotonic, and volume overload with these may manifest with pulmonary and cerebral edema. Alternatively, hypotonic fluids such as glycine and sorbitol solutions also may intravasate, but large amounts may lead not only to hypervolemia but also to electrolyte dilution, specifically hyponatremia. Mechanistically, glycine and sorbitol are both metabolized following absorption, effectively leaving free water in the intravascular space. Normal serum sodium levels are 135 to 145 mEq/L, and levels below this may lead to seizure followed by respiratory arrest. In addition, hypokalemia and hypocalcemia often can develop concurrently.

Therefore, in patients in whom large fluid volume deficits are reached, measurement of serum electrolyte levels is warranted. If a serum sodium level lower than 125 mEq/L is reached, care should be continued in a critical care setting. Treatment includes stimulation of diuresis with furosemide (Lasix) 20 to 40 mg given intravenously and correction of hyponatremia with 3-percent sodium chloride administered 1 to 1.5 mEq/L per hour. The goal of therapy is to reach a serum sodium level of 135 mEq/L within 24 hours. Overcorrection is avoided to prevent additional cerebral effects (Baggish, 2005).

To assist with fluid volume calculation, most operative hysteroscopes contain continous-flow systems that allow fluid deficits to be calculated. Volume deficits are calculated by the amount of distending media delivered subtracted by the amount returned through collection. Determination of deficits should be performed every 15 minutes during procedures. If a procedure has the potential for larger deficits, a Foley catheter is also warranted for urine output monitoring. The American Association of Gynecologic Laparoscopists recommends that if fluid discrepancy reaches 750 mL, a surgeon should plan for completion of the case. If fluid deficits reach 1,500 mL of a nonelectrolyte solution or 2,500 mL of normal saline, the procedure is concluded immediately, electrolytes measured, and diuretics given as indicated (Loffer, 2000).

Hysteroscopic Electrosurgery

Most hysteroscopic tissue resection or desiccation relies on monopolar current. Because current is dissipated and thus is ineffective in electrolyte solutions, these techniques typically have required nonelectrolyte solutions such as sorbitol, mannitol, and glycine.

However, as discussed earlier, these media can be associated with hyponatremia if fluid volume overload develops. Alternatively, a bipolar electrosurgery system (Versapoint Bipolar Electrosurgery System, Ethicon, Somerville, NJ) allows use of traditional hysteroscopic tools in a saline solution.

SURGICAL COMPLICATIONS

Uterine Perforation

In addition to fluid overload, uterine perforation or bleeding may complicate hysteroscopic procedures. The uterus may be perforated during uterine sounding, cervical dilation, or hysteroscopic procedures (Cooper, 2000). Fundal perforations created by sounds, dilators, or hysteroscopes can be managed conservatively because the myometrium typically will contract around these defects. In contrast, because lateral perforation may injure larger pelvic vessels, posterior perforation may injure the rectum, and perforation caused by electrosurgical tools may cause organ laceration or burn, diagnostic laparoscopy is warranted in these patients. Similarly, anterior perforations should prompt cystoscopy to evaluate associated bladder injury.

Hemorrhage

Heavy bleeding may develop during or following resection procedures. Although hysteroscopic electrosurgical electrodes may be used to contact and coagulate smaller vessels, these may be less effective for larger vessels.

If heavy bleeding is encountered and is refractory to electrosurgical coagulation, termination of the procedure may be indicated. A Foley catheter balloon can be placed into the endometrial cavity and inflated incrementally with 5 to 10 mL of saline until moderate resistance to catheter tension is noted. An attached collection bag can be used to document blood loss and bleeding cessation, at which point the catheter may be removed.

Surgical Steps

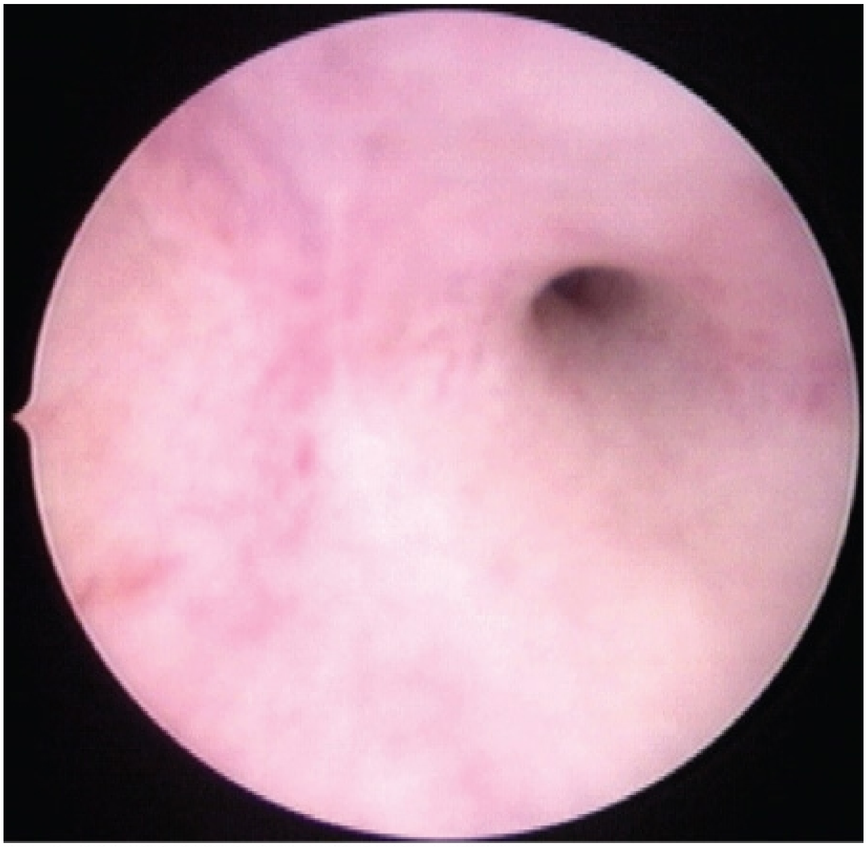
1. **Anesthesia and Patient Positioning.** Diagnostic hysteroscopy can be performed in an outpatient setting under local analgesia with or without intravenous sedation. Alternatively, a day-surgery setting and general anesthesia may be selected.

   The patient is placed in a dorsal lithotomy position, and the vagina is surgically prepared. Because diagnostic hysteroscopy is a short procedure with little, if any, blood loss, CO_2 or a saline typically is selected for uterine distension.

2. **Hysteroscope Introduction.** For most diagnostic hysteroscopic procedures, cervical dilation is not required to admit the 4- to 5-mm hysteroscope. A single-toothed tenaculum is placed on the anterior cervical lip, the flow of distention medium is begun, and the hysteroscope is introduced into the endocervical canal. Pressure exerted by the distention medium opens the endocervical canal and allows hysteroscope entry.

3. **Hysteroscopic Evaluation.** As the hysteroscope is inserted, the endocervical canal is examined for abnormalities. On entering the cavity, the hysteroscope is held at the distal portion of the cavity to allow a panoramic evaluation. Systematically, the hysteroscope is moved to the fundus and then to the left and right to permit inspection of the tubal ostia (Fig. 41-35.4).

FIGURE 41-35.4



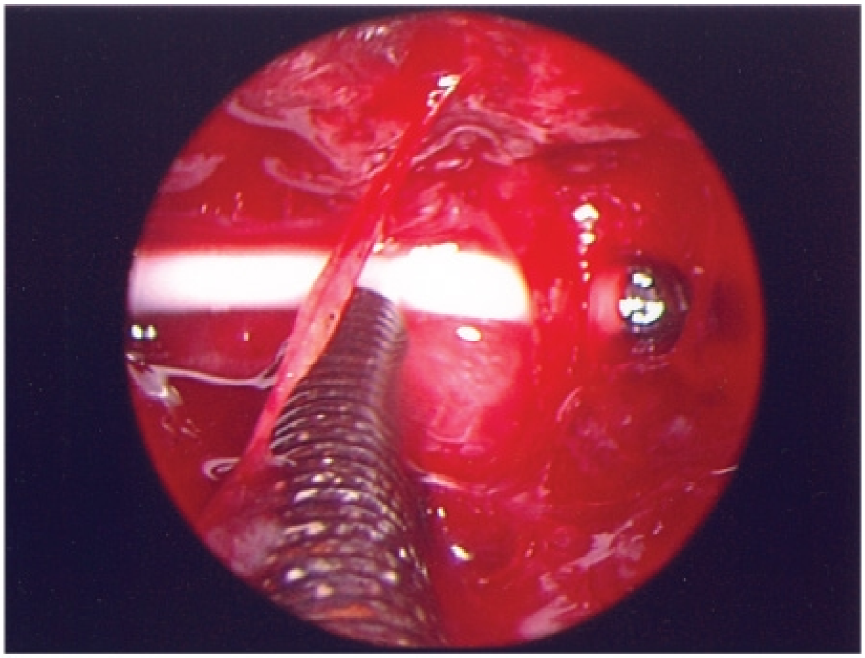
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Hysteroscopic photograph of normal tubal ostia. (Courtesy of Dr. Kevin Doody.)

4. **Specific Procedures.** After complete inspection, if specific lesions are identified, they typically are biopsied with hysteroscopic forceps.

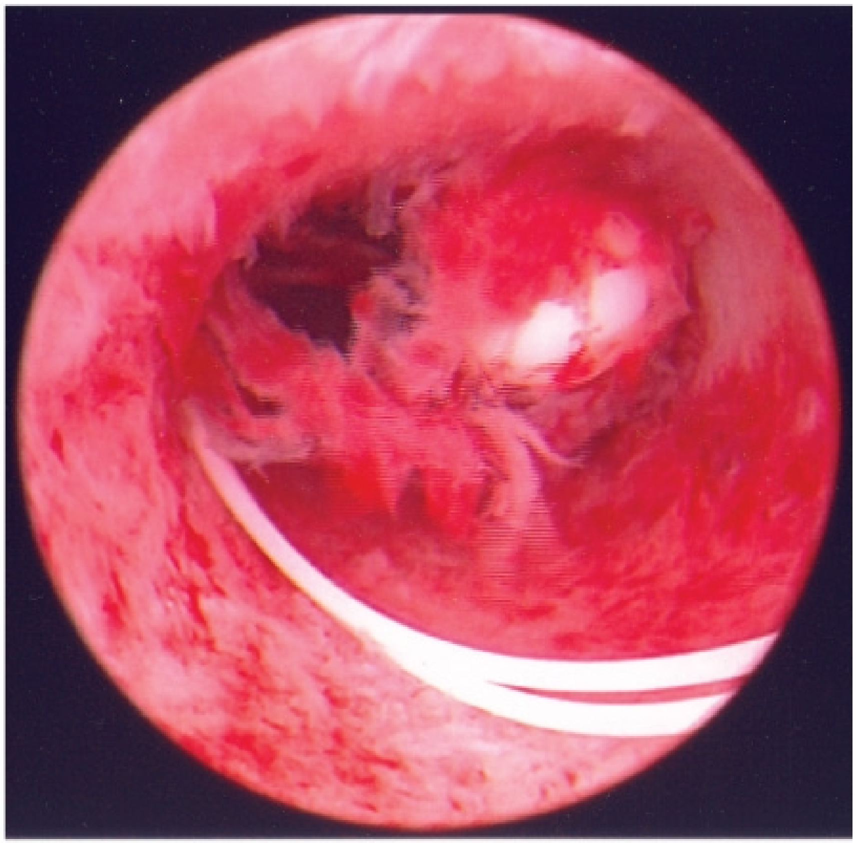
   If intrauterine device (IUD) removal is planned, most are grasped by the string or stem with hysteroscopic forceps and are extracted easily as the entire hysteroscope is removed (Fig. 41-35.5). However, embedded or fragmented devices may require removal in pieces. In these instances, a sturdy portion of the IUD is grasped firmly, and traction on the forceps is exerted toward the vagina. For patients in whom the IUD is deeply embedded, laparoscopy can assist in identifying uterine perforation and in determining whether the device is best removed hysteroscopically or laparoscopically.

FIGURE 41-35.5



A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Hysteroscopic photograph of retained copper intrauterine device prior to endoscopic removal. **A.** Copper coils around IUD body and white IUD crossbar are seen. **B.** Two white IUD strings and white, ball-shaped tip of IUD body is seen. (Courtesy of Dr. Karen Bradshaw.)

5. **Procedure Completion.** At the end of the procedure, the flow of distending medium is stopped, and hysteroscope and tenaculum are removed.

Postoperative

Patient recovery typically is rapid and without complication and mirrors that following dilatation and curettage. Diet and activities may be resumed as desired by the patient. Spotting or light bleeding is not uncommon and typically stops within days.

41-36 ENDOMETRIAL ABLATION PROCEDURES

Endometrial ablation broadly describes a group of hysteroscopic procedures that destroys or resects the endometrium and for many women, serves as an effective treatment of abnormal uterine bleeding. Within the ablation group, techniques are defined as *first-* or *second-generation* depending on their temporal introduction into use and the need for hysteroscopic skills. First-generation tools require advanced hysteroscopic skills and longer operating times and can be associated with distention media complications. These techniques include endometrial desiccation with the neodymium:yttrium-aluminum-garnet (Nd-YAG) laser, rollerball electrosurgical desiccation, and endometrial resection by resectoscope.

With comparison of first-generation methods, it appears that all three produce similar outcomes in terms of decreased uterine

bleeding and patient satisfaction. However, resection methods have been associated with more surgical complications, and thus desiccation methods within this group may be preferred for women without intracavitary lesions (Lethaby, 2002; Overton, 1997).

To obviate skill requirements and risks of these early ablative tools, second-generation methods have been introduced over the last 10 years. These tools use a variety of modalities to ablate the endometrium, including thermal energy, cryosurgery, electrosurgery, and microwave energy, but without the need for direct hysteroscopic guidance.

Preoperative

PATIENT EVALUATION

Prior to ablation, complete evaluation of abnormal uterine bleeding should be completed. Accordingly, the possibility of pregnancy, endometrial cancer, and active pelvic infection should be excluded. During evaluation of bleeding, transvaginal sonography (TVS), saline-infusion sonography (SIS), and hysteroscopy may be used solely or in combination (see Chap 8, Endometrial Biopsy). However, because many second-generation ablation techniques require a normal endometrial cavity, and because endometrial pathology, if identified, can be treated concurrently by several of the ablative methods, SIS or hysteroscopy is preferred for preoperative evaluation.

CONSENT

Patients selecting ablation should be aware of success rates relative to other treatment options for abnormal bleeding, as discussed in Chapter 8, Endometrial Destructive Procedures. In general, rates of decreased flow range from 70 to 80 percent, and of amenorrhea, from 15 to 35 percent. Therefore, a patient should not undergo ablation if guaranteed amenorrhea is a treatment goal. In addition, endometrial ablation effectively destroys the endometrium and is contraindicated in those who desire future fertility.

Complications associated with ablation mirror those with operative hysteroscopy, although the risk of fluid volume overload is avoided with second-generation tools.

PATIENT PREPARATION

During hysteroscopic surgeries, bacteria in the vagina may gain access to the upper reproductive tract and peritoneal cavity. Although there are no strong evidence-based data to support the use of prophylactic antibiotics, their use seems reasonable with these surgeries. We typically administer cefazolin 2 g intravenously immediately prior to surgery.

Because the endometrium can thicken from only a few millimeters in the early proliferative phase to deeper than 10 mm in the secretory phase, all first-generation techniques and some second-generation techniques should be performed in the early proliferative phase. Otherwise, drugs that induce endometrial atrophy such as gonadotropin-releasing hormone (GnRH) agonists, combination oral contraceptives, or progestins may be used for 1 to 2 months prior to surgery, or curettage may be performed immediately prior to surgery.

Intraoperative

Surgical Steps

1. **Anesthesia and Patient Positioning.** Endometrial ablation typically is a day-surgery procedure performed under general anesthesia. The patient is positioned in the dorsal lithotomy position, and the perineum and vagina are surgically prepped.

2. **Selection of Distending Medium.** With first-generation procedures, distending medium is required and selected based on the destructive energy used (see Section 41-35, Hysteroscopy). In general, saline may be used for laser and bipolar electric current, whereas monopolar tools require nonelectrolyte solutions.

3. **Neodymium:Yttrium-Aluminum-Garnet (Nd:YAG) Laser.** Introduced in the 1980s, the Nd:YAG laser was the first ablative tool. Under direct hysteroscopic observation and uterine distention with saline, an Nd:YAG laser fiber touches the endometrium and is dragged across the endometrial surface to create furrows of photocoagulated tissue 5 to 6 mm in depth (Garry, 1995; Goldrath, 1981).

4. **Trancervical Resection of the Endometrium (TCRE).** In attempts to lower cost from expensive laser equipment, transcervical resection of the endometrium (TCRE) was developed (DeCherney, 1983, 1987). In addition to less expense, because of the larger loop diameter, TCRE can be completed more quickly than ablation with a laser fiber and thereby can reduce the risk of excess medium absorption.

   This procedure uses a resectoscope with monopolar or bipolar electric current to excise strips of endometrium. The resection technique is similar to that described for hysteroscopic myomectomy, as discussed in Section 41-37, Hysteroscopic Myomectomy. Excised tissue strips are sent for pathologic evaluation (Garry, 1995; Lethaby, 2002; Vilos, 2004). Moreover, in patients with concurrent intrauterine pathology such as endometrial polyps or submucous leiomyomas, TCRE can excise these lesions in addition to the endometrium.

   However, TCRE has been associated with higher rates of perforation, especially at the cornual areas, where the myometrium is thinner. For this reason, many use a rollerball electrosurgical electrode in combination with TCRE, with the rollerball used in the cornual region (Oehler, 2003).

5. **Rollerball.** A 2- to 4- mm ball- or barrel-shaped electrosurgical electrode can be rolled across the endometrium as an effective means of vaporizing the endometrium (Vancaillie, 1989). Advantages to rollerball ablation compared with TCRE include shorter operating time, less fluid absorption, and lower rate of perforation. Unfortunately, it is not effective in the treatment of intracavitary lesions, and pathology specimens are not obtained.

6. **Thermal Balloon Ablation.** The first thermal balloon ablation system was used in the early 1990s. Since its introduction, several thermal balloon ablation systems are currently used worldwide (Fig. 41-36.1). The ThermaChoice III Uterine Balloon Therapy System (Gynecare, Division of Ethicon, Somerville, NJ) is approved for use in the United States, but not the Cavaterm Plus System (Wallsten Medical SA, Morges, Switzerland) or the Thermablate Endometrial Ablation System (MDMI Technologies, Richmond, BC, Canada).

   The ThermaChoice III Uterine Balloon Therapy System is a software-controlled device designed to ablate endometrial tissue using thermal energy. A 5-percent dextrose and water solution is instilled into a disposable silicone balloon and heated to coagulate the endometrium. During treatment, the fluid within the balloon is circulated to maintain a temperature of 87Â°C (186Â°F) for 8 minutes. The balloon can be introduced without hysteroscopic assistance into the uterine cavity and when inflated, conforms to the cavity contour.

   All hot-liquid balloon devices require no advanced hysteroscopic skills, and complication rates are low (Gurtcheff, 2003; Vilos, 2004). Disadvantages include the requirement of an anatomically normal uterine cavity and of pharmacologic thinning prior to thermal ablation. Alternatively, mechanical thinning can be accomplished with dilatation and curettage prior to ablation.

FIGURE 41-36.1

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

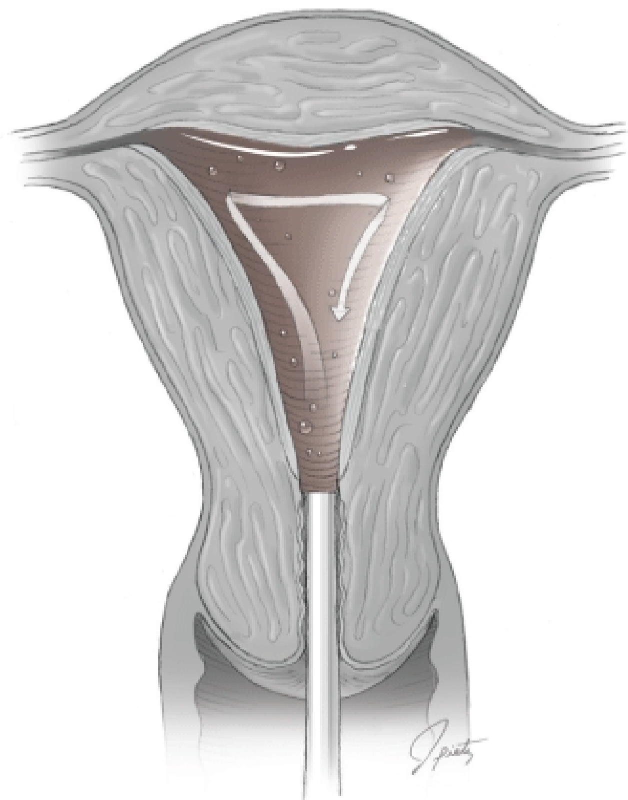
ThermaChoice III Uterine Balloon Therapy System. (Courtesy of Gynecare.)

7. **Hysteroscopic Thermal Ablation.** Several second-generation ablation procedures require a normal uterine cavity. However, the HydroThermAblator (HTA) (Boston Scientific, Natick, MA) system allows treatment of the endometrium concurrent with submucous leiomyomas, polyps, or abnormal uterine contour.

   This tool is designed to ablate the endometrial lining of the uterus by heating an uncontained saline solution to a temperature of 90Â°C and recirculating it through the uterus for 10 minutes (Fig. 41-36.2). Spill through the fallopian tubes is avoided because hydrostatic pressure during the procedure remains below 55 mm Hg, which is well below pressures needed to open the tubes. Similarly, the water seal created between the hysteroscope and the internal cervical os prevents leakage of fluid into the vagina. For this reason, care should be taken not to dilate the cervix to a diameter greater than 8 mm. Additionally, preoperative laminaria are not recommended.

   Initially, a hysteroscope is inserted into the 7.8-mm-diameter disposable HTA sheath. This combination is introduced into the endometrial cavity to enable visualization while room-temperature saline is instilled into the uterine cavity. The fluid then is heated gradually and circulated to treat the endometrium. At completion of the treatment phase, cool saline solution replaces the heated fluid, and the instrument then is removed (Glasser, 2003).

FIGURE 41-36.2

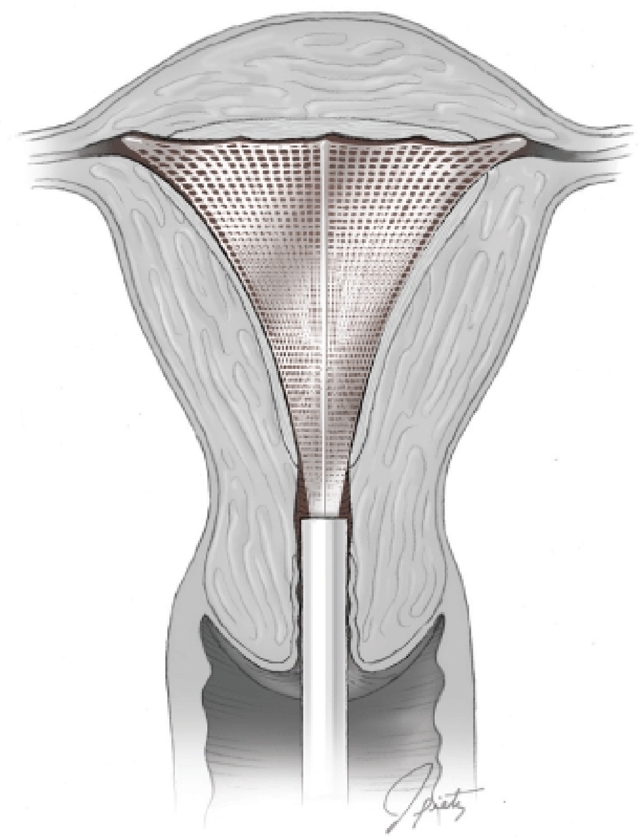


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Hysteroscopic thermal ablation.

8. **Impedance-Controlled Electrocoagulation.** The NovaSure Endometrial Ablation System (Cytyc Corp, Marlborough, MA) was approved for marketing in the United States in 2001. The system consists of a high-frequency (radiofrequency) electrosurgical generator and a single-use three-dimensional, metal, fabric-like mesh that is designed to contour to the shape of the endometrial cavity. During treatment, an attachment provides suction to firmly draw the endometrium and myometrium up against the mesh electrode for improved contact and to remove generated vapor (Fig. 41-36.3).

FIGURE 41-36.3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Impedance-controlled electrocoagulation.

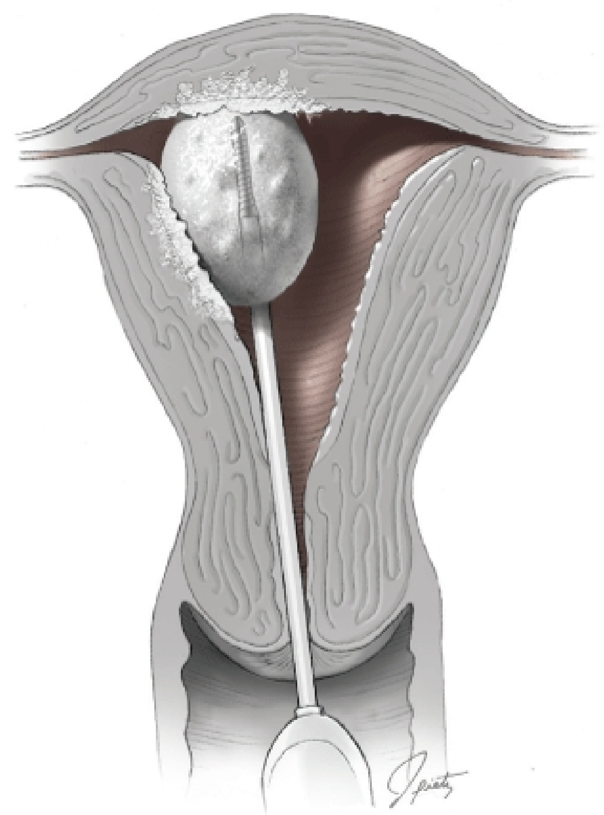
9. **Microwave Ablation (MEA).** Approved in 2003 for use in the United States, the Microwave Endometrial Ablation (MEA) Technique (Microsulis Plc, Waterlooville, Hampshire, UK) uses microware energy to destroy the endometrium. During the procedure, a microwave probe is inserted until the tip reaches the uterine fundus. Once inserted, the probe tip is maintained at 75 to 80Â°C and moved slowly from side to side. Microwave energy is spread with a maximum penetration of 6 mm over the entire surface of the uterine cavity. Speed is an advantage, with the entire treatment completed in 2 to 3 minutes (Cooper, 1999).

10. **Cryoablation.** In addition to thermal damage, endometrial ablation can be achieved with extreme cold. The Her Option (American Medical Systems, Minnetonka, MN) Cryoablation System was approved for use in the United States in 2001. Similar to the physics of cervical cryotherapy, gases compressed under pressure with this unit can generate temperatures of â€"100 to â€"120Â°C at the cryoprobe tip to produce an iceball. As the iceball grows, its leading edge advances through tissue, and cryonecrosis develops in those tissues, reaching temperatures less than â€"20Â°C (see Section 41-13, Treatment of Ectocervical Preinvasive Lesions).

    The Her Option Cryoablation System contains a metal probe that is covered by a 5.5-mm disposable cryoprobe. After dilation of the cervix, the cryoprobe's 1.4-inch cryotip is placed against one side of the endometrial cavity and advanced to the uterine cornua (Fig. 41-36.4). Concurrent transabdominal sonography is required to ensure accurate cryotip placement and surveillance of the increasing iceball diameter, which is seen sonographically as an enlarging hypoechoic area (American

Medical Systems, 2006). The first freeze is terminated after 4 minutes or sooner if the advancing iceball reaches to within 3 mm of the uterine serosa. The cryotip is allowed to warm, is removed from the cornua, and is redirected into the contralateral cornua. A second freeze is performed for 6 minutes.

FIGURE 41-36.4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Cryoablation.

Postoperative

Advantages to endometrial ablation include rapid patient recovery and low incidence of complications. Patients may resume normal diet and activities as tolerated. Patients may expect light bleeding or spotting during the first postoperative days as necrotic endometrial tissue is shed. A serosanguineous discharge follows for 1 week and is replaced by a profuse and watery discharge for another 1 to 2 weeks.

As mentioned earlier, ablation has been associated with subsequent pregnancy complications, such as placenta accreta, preterm labor, and spontaneous abortion (Cook, 2003; Hare, 2005). Thus, in women with reproductive function, a reliable contraceptive method must be used following surgery. In many instances, a sterilization procedure may be performed concurrently with ablation.

41-37 HYSTEROSCOPIC MYOMECTOMY

For symptomatic women with submucous leiomyomas, hysteroscopic resection of these tumors may provide relief of symptoms in most cases. Candidates may include those with abnormal uterine bleeding or those with infertility in whom leiomyomas are

suspected to be contributory. Those tumors selected for resection should be either submucous or intramural with a prominent submucous component. During surgery, pedunculated submucous leiomyomas may be excised similarly to polyps, as described in Section 41-41, Lysis of Intrauterine Adhesions. However, those with an intramural component require resection with a resectoscope, morcellator, or laser.

Preoperative

PATIENT EVALUATION

Hysteroscopic myomectomy is a safe and effective option for most women. Contraindications to surgery, however, include pregnancy, potential endometrial cancer, current reproductive tract infection, and medical conditions sensitive to fluid volume overload.

Specific leiomyoma characteristics such as increasing size, number, and degree of intramural penetration can raise the technical difficulty, complication rate, and clinical failure rate of this procedure. Thus, prior to resection, women should undergo saline-infusion sonography (SIS) or hysteroscopy to evaluate leiomyoma characteristics. Alternatively, magnetic resonance (MR) imaging also can accurately document uterine anatomy, but its expense and availability may limit its routine use.

During SIS evaluation, leiomyomas may be grouped according to criteria from the European Society of Hysteroscopy:

- Class 0: Complete submucosal location
- Class I: Greater than 50 percent submucosal component
- Class II: Some submucosal involvement but greater than 50 percent myometrial component

Large or predominantly intramural tumors decrease clinical success rates and increase surgical risks and the need for more than one surgical session to complete resection. For these reasons, many choose to resect only type 0 and type I tumors and those measuring less than 3 cm (Vercellini, 1999; Wamsteker, 1993).

CONSENT

In general, complications of this procedure mirror those for hysteroscopy, and rates of 2 to 3 percent have been reported (see Section 41-35, Hysteroscopy). However, hysteroscopic myomectomy is associated with a greater risk of uterine perforation. This complication may follow cervical dilatation but more frequently results during aggressive resection into the myometrium. Because of this risk, women also should be consented for diagnostic laparoscopy.

Additionally, patients planning to seek pregnancy should be aware of possible intrauterine adhesion formation following resection and of rare uterine rupture during subsequent pregnancies (Batra, 2004; Howe, 1993).

Women with type I or type II tumors or those with large leiomyomas should be counseled that a second surgery may be required to finish resections that may have been halted due to advancing fluid volume deficits. Fortunately, because of newer hysteroscopic morcellating tools, operating times and thus fluid deficits are decreased, even with large tumors. Additionally, although myomectomy is an effective treatment, 15 to 20 percent of patients eventually will require reoperation, either hysterectomy or repeat hysteroscopic resection, at a later time for either persistent or recurrent symptoms (Derman, 1991; Hart, 1999).

PATIENT PREPARATION

As discussed in Chapter 9, GnRH Agonists, gonadotropin-releasing hormone (GnRH) agonists can shrink leiomyomas preoperatively to enable resection of large tumors or allow patients to rebuild their red cell mass before surgery. Advantages and disadvantages of these drugs warrant individualization of their use (Table 41-37.1).

Table 41-37.1 Factors that Affect the Decision to Use Gonadotropin-Releasing Hormone Agonists Prior to Hysteroscopic Myomectomy		
Parameter	**Disfavoring Pretreatment**	**In Favor of Pretreatment**
Anemia	None or mild	Pronounced
Type of myoma	Types 0 and I	Type II
Diameter	<2 cm	>3 cm
Residual distance to the serosa	>10 mm	<8 mm
Number of leiomyomas	Single	Multiple
Leiomyoma location	Anterior, posterior, and lateral wall	Fundus, close to tubal ostium
Ability of the surgeon	Highly skilled	Less skilled

Adapted from Brandner, 2000, with permission.

To allow easier cervical dilatation and resectoscope insertion, laminaria tents may be place the evening prior to surgery. Alternatively, misoprostol also has ben shown to aid dilatation in some but not all studies, and postmenopausal women may benefit less from this pretreatment (Ngai, 2001; Preutthipan, 2000). We typically prescribe misoprostol 100 µg orally the evening prior to and the morning of surgery.

Although the risk of postoperative infection is low, because pelvic infections can have devastating effect on future fertility, most surgeons recommend antibiotic prophylaxis prior to extensive hysteroscopic resections, as with myomectomy.

CONCURRENT ABLATION

In women with menorrhagia and with no desire for future fertility, endometrial ablation may be performed concurrently (see Section 41-36, Endometrial Ablation Procedures) (Loffer, 2003). However, because leiomyoma resection alone will correct abnormal bleeding in most women, we do not perform adjunctive endometrial ablation routinely unless the patient desires hypomenorrhea.

Intraoperative

INSTRUMENTS

Hysteroscopic myomectomy can be performed using a resectoscope or hysteroscopic morcellator. Both procedures will be described.

Surgical Steps

1. **Anesthesia and Patient Positioning.** For most patients, hysteroscopic myomectomy is an outpatient procedure performed under general anesthesia. The patient is placed in dorsal lithotomy position, the vagina is surgically prepared, and a Foley catheter is placed.

2. **Medium Selection.** The choice of distending medium is dictated by the resecting tool used. Resection using a morcellator, bipolar electrosurgical loop, or laser can be performed in saline solution. Alternatively, cases using a monopolar electrosurgical loop require an electrolyte-free solution (see Section 41-35, Hysteroscopy).

3. **Cervical Dilatation.** Using Pratt or other suitable dilators, the surgeon dilates the cervix as described in Section 41-16, Sharp Dilatation and Curettage.

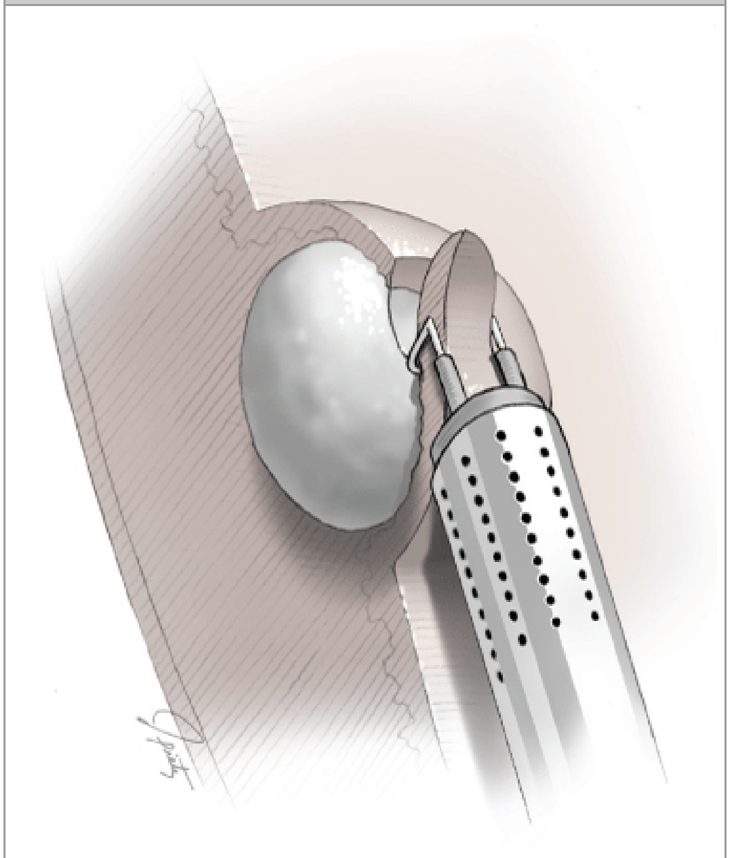
4. **Instrument Insertion.** The distending medium flow is begun, and the resectoscope or morcellator is inserted into the endocervical canal under direct visualization. On entering the endometrial cavity, a panoramic inspection is performed first to

identify leiomyomas.

5. **Resection.** The electrosurgical unit is set to a continuous-wave mode (cutting). The resectoscope loop is advanced to lie behind the leiomyoma, and electric current is applied before the loop contacts the tissue. To minimize thermal injury and perforation, current should be applied only as the loop is retracted and not when it is being extended. On contact, the loop electrode is retracted toward the resectoscope (Fig 41-37.1). To ensure a clean cut and complete excision of the shaved strip, current is not stopped until the entire loop is retracted. The shaved strip of smooth muscle floats within the endometrial cavity.

   This shaving process is repeated serially toward the leiomyoma's base until the tumor is removed. Although strips can be removed from the cavity after each pass, this results in a repetitive loss of uterine distention. Repeated removal and reinsertion of a resectoscope increase the risk of perforation and fluid intravasation. Thus, in most cases, pushing removed strips to the fundus will help to clear the operative field adequately. However, if the view becomes obstructed, a pause in resection may be required to remove these strips.

FIGURE 41-37.1



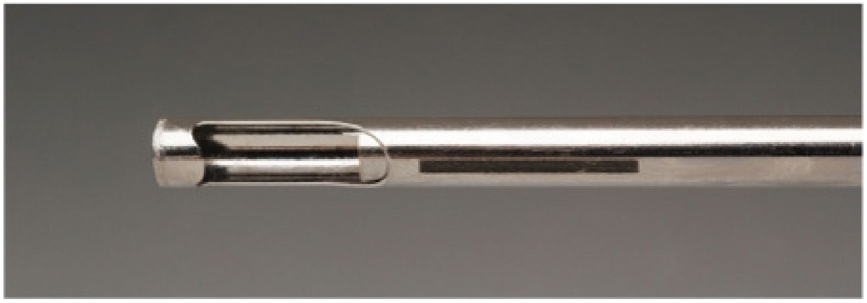
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Hysteroscopic resection.

6. **Morcellation.** The Intra Uterine Morcellator (IUM, Smith & Nephew Endoscopy, Andover, MA) consists of two hollow, rigid, disposable tubes that fit within one another (Fig. 41-37.2). The inner tube rotates within the outer and is driven mechanically by an electrically powered control unit. The IUM for leiomyomas has a reciprocating cutting action with an optimal

performance at 1,100 rotations per minute (rpm). By means of a vacuum source connected to the inner tube, tissue is suctioned into the window opening at the tip of the device and is shaved off as the inner tube rotates. Suction also removes morcellated tissue through the device and allows collection in a net bag for pathologic analysis. When rotation of the inner tube is not activated, the morcellator window opening is always closed to prevent suction of distention fluid, uterine cavity collapse, and risk of perforation. In retrospective comparisons, hysteroscopic morcellation is faster than resectoscopy and appears easier to perform. It is associated with fewer fluid-related complications and a shorter learning curve than conventional resectoscopy (Emanuel, 2005).

FIGURE 41-37.2

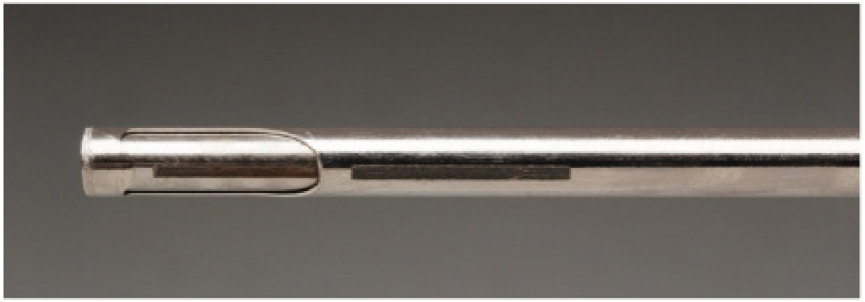


A

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



C

Hysteroscopic morcellator. **A.** Morcellator blade retracted. Suction draws tissue into the fluted opening. **B.** Blade partially advanced. The blade rapidly rotates as it is advanced and retracted **C.** Blade is fully advanced and slices tissue drawn into the opening.

7. **Intramural Leiomyomas.** During removal of leiomyomas with an intramural component, uterine perforation risks are increased if resection extends below the level of the normal myometrium. Therefore, when resection reaches this level, the surgeon should pause and wait for the surrounding myometrium to contract around the now smaller tumor and deliver deeper portions of the leiomyoma into the uterine cavity (see Fig. 41-37.1).

8. **Fluid Volume Deficit.** Because of the risk of hypervolemia during hysteroscopic myomectomy, fluid volume deficit should be monitored carefully, as discussed in Section 41-35, Hysteroscopy.

9. **Hemostasis.** Bleeding is common during myomectomy, and vessels may be coagulated with the edge of the resecting loop with the electrosurgical unit set to a coagulating current. At times, a ball electrode may be required to increase the surface area over which current is delivered. Rarely, hemorrhage may not be controlled with electrosurgical means. In these cases, mechanical pressure applied to bleeding vessels by a Foley balloon inflated with 5 to 10 mL of saline may be required.

Postoperative

Recovery following myomectomy is quick and typically without complication. Patients may resume diet and activities as tolerated. Spotting or light bleeding may follow surgery for 1 to 2 weeks.

For patients desiring pregnancy, conception may be attempted in the menstrual cycle after the resection unless the leiomyoma was broad based or had a significant intramural component. In these patients, barrier contraception is advised for three cycles. For women who fail to conceive or continue to have abnormal bleeding following resection, postoperative hysterosalpingography or hysteroscopy is recommended.

41-38 POLYPECTOMY

Indications for the removal of endometrial polyps include abnormal uterine bleeding, infertility, and risk of malignant transformation (see Chap. 8, Endometrial Polyp). Hysteroscopic excision of these growths may be completed by incision of the polyp base with hysteroscopic scissors or resectoscope loop, avulsion of the polyp with hysteroscopic forceps, or morcellation. Of these, the resectoscope and morcellator offer the most versatility in managing lesions, both large and small.

Preoperative

PATIENT EVALUATION

In many women undergoing polypectomy, preoperative transvaginal sonography or saline-infusion sonography have been completed, and information regarding the size, number, and location of polyps should be reviewed prior to surgery (see Figs. 8-7

and 8-8).

CONSENT

The complication rates for this procedure are low and mirror those for hysteroscopy in general (see Section 41-35, Hysteroscopy) (Jansen, 2000).

PATIENT PREPARATION

As with most hysteroscopic procedures, polypectomy ideally is performed during the follicular phase of the menstrual cycle when the endometrial lining is thinnest and polyps would be most easily identified. The need for antibiotic prophylaxis is unclear and may be left to surgeon discretion.

Intraoperative

INSTRUMENTS

As described earlier, a resectoscope with a 90-degree loop electrode is ideal for polyp excision. Alternatively, an intrauterine morcellator also can quickly excise even large growths.

Surgical Steps

1. **Anesthesia and Patient Positioning.** Although simple polypectomy procedures, under local analgesia in an office setting, have been described, most are outpatient procedures performed under general anesthesia. Following administration of adequate anesthesia, the patient is placed in dorsal lithotomy position, the vagina is surgically prepared, and a Foley catheter is placed.

2. **Media Selection.** Hysteroscopic morcellation is performed with a physiologic saline solution. If a monopolar resectoscope is used, then a nonelectrolyte solution is required (see Section 41-35, Hysteroscopy). Alternatively, selection of a bipolar resecting system (Versapoint, Ethicon, Somerville, NJ) allows performance within saline. As with any hysteroscopic procedure, fluid volume deficits are calculated and noted every 15 minutes during surgery.

3. **Cervical Dilatation.** The larger diameter of an 8- or 10-mm resectoscope or morcellator typically requires dilatation up to 9 mm with Pratt or other similar dilators.

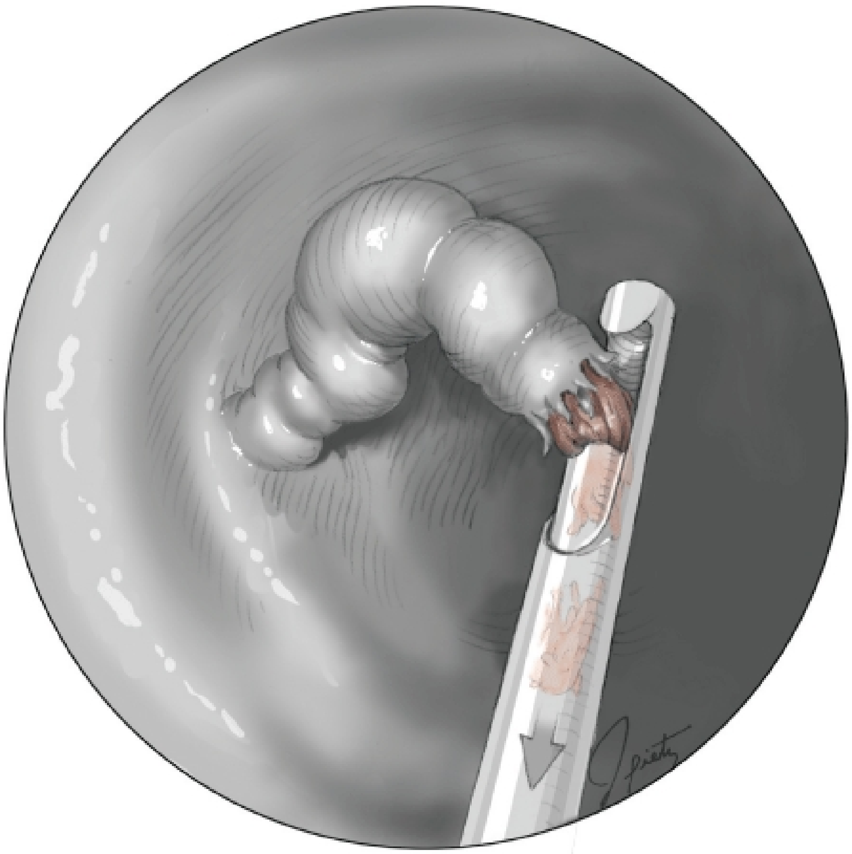
4. **Resection.** Medium flow is begun, and the resectoscope is inserted into the endocervical canal under hysteroscopic visualization. On entering the cavity, a panoramic inspection is completed to identify the location and number of polyps. The resectoscope loop then is extended to reach behind the polyp. Electrosurgical current is applied as the loop is retracted toward the cervix to cut the polyp base. The freed polyp then is grasped and delivered through the cervical os.

   In patients in whom the polyp is large, several passes with the loop electrode may be required for complete excision. Passes begin at the polyp tip and progress until the base is reached.

5. **Morcellation.** As with loop resection, saline solution flow is begun, and the morcellation unit is inserted. During morcellation, it is important to work from the polyp periphery toward the base (Fig. 41-38.1). Moreover, the tumor should be kept between the morcellator opening and the optics of the camera.

   The morcellator has suction action as well. This can be used apart from its cutting effects to clear blood, tissue dÃ©bris, and clots during resection of large growths.

FIGURE 41-38.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Hysteroscopic polypectomy.

6. **Control of Bleeding.** Bleeding sites may be coagulated with the same resection loop using a coagulating current. For heavy bleeding, a Foley catheter balloon may be inflated as described in Surgical Steps.

7. **Instrument Removal.** The resectoscope or morcellator is removed, and the surgical specimen is sent for pathologic evaluation.

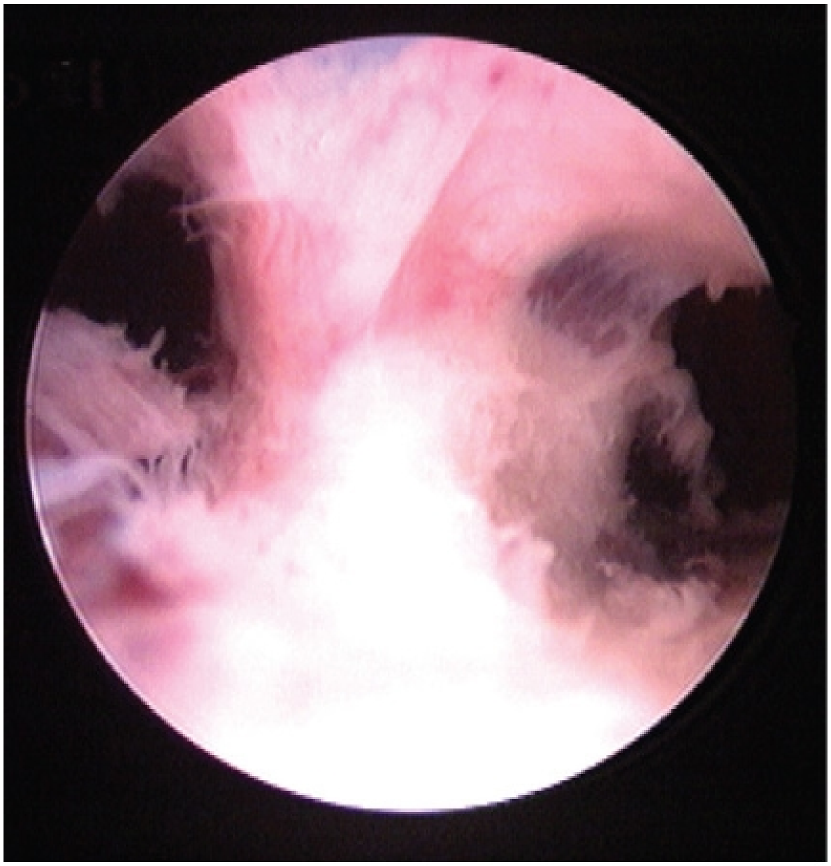
Postoperative

Recovery following polypectomy is rapid, is typically without complication, and follows that for other hysteroscopic procedures (see Section 41-35, Hysteroscopy).

41-39 SEPTOPLASTY

A uterine septum typically results from incomplete medial regression of the mÃ¼llerian ducts during their fusion (Fig. 41-39.1; see also Chap 18, Gonadal Differentiation). These septa have been associated with increase rates of first- and second-trimester spontaneous abortion, and this serves as the main indication for septum excision. Before the popularity of operative hysteroscopy, septoplasty was performed abdominally and with a hysterotomy incision. Fortunately, hysteroscopic septoplasty affords decreased morbidity to the patient and uterus and currently is preferred.

FIGURE 41-39.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Hysteroscopic photograph of uterine septum. (Courtesy of Dr. Kevin Doody.)

Preoperative

PATIENT EVALUATION

Diagnosis of the septate uterus is outlined in Chapter 18, Diagnosis and Treatment, and includes hysterosalpingography (HSG) and sonography. Because of the frequent association between renal and mÃ¼llerian anomalies, intravenous pyelography is also performed. Finally, although a septate uterus is associated with infertility and pregnancy loss, evaluation for other causes of these two conditions should be completed prior to septum excision. Contraindications to septoplasty include pregnancy and active pelvic infection, and these should be excluded.

CONSENT

Hysteroscopic septoplasty is a safe and effective method of treatment for pregnancy loss, and postoperative live birth rates approximate 85 percent (Fayez, 1986).

In general, complications mirror those for operative hysteroscopy, although the risk of uterine perforation appears increased. For this reason, concurrent laparoscopy is recommended with this procedure to help inform a surgeon as to the proximity of the uterine serosa. As the hysteroscope nears the fundal serosa, transillumination via the hysteroscope light indicates the potential for uterine perforation. Accordingly, a patient should be consented for concurrent diagnostic laparoscopy, as outlined in Section 41-28, Laparoscopy.

PATIENT PREPARATION

As with most operative hysteroscopic procedures, antibiotic prophylaxis is warranted. A first- or second-generation cephalosporin or other suitable antibiotic is appropriate. Additionally, laminaria tents or misoprostol may be used preoperatively to ease cervical dilatation (see Section 41-35, Hysteroscopy).

Intraoperative

INSTRUMENTS

Septum resection may be completed using hysteroscopic scissors, resectoscope loop, or neodymium:yttrium-aluminum-garnet (Nd:YAG) laser. Selection is based on surgeon preference and skill.

Surgical Steps

1. **Anesthesia and Patient Positioning.** Hysteroscopic septoplasty typically is a day-surgery procedure performed under general anesthesia. Because concurrent laparoscopy is recommended, a woman is placed in the dorsal lithotomy position, the abdomen and vagina are surgically prepared, and a Foley catheter is inserted.

2. **Medium Selection.** The choice of distending medium is dictated by the incising tool used. Sharp incision with scissors, Nd:YAG laser, or bipolar instrument is commonly selected and can be performed in any liquid medium (see Section 41-35, Hysteroscopy).

3. **Concurrent Laparoscopy.** Because of the increased risk of uterine perforation, adjunctive laparoscopy is warranted. Placement of the laparoscope follows the steps described in Section 41-28, Laparoscopy.

4. **Cervical Dilatation.** A tenaculum is placed on the anterior cervical lip. Using a Pratt or other suitable dilator, the surgeon dilates the cervix as described in Section 41-16, Sharp Dilatation and Curettage.

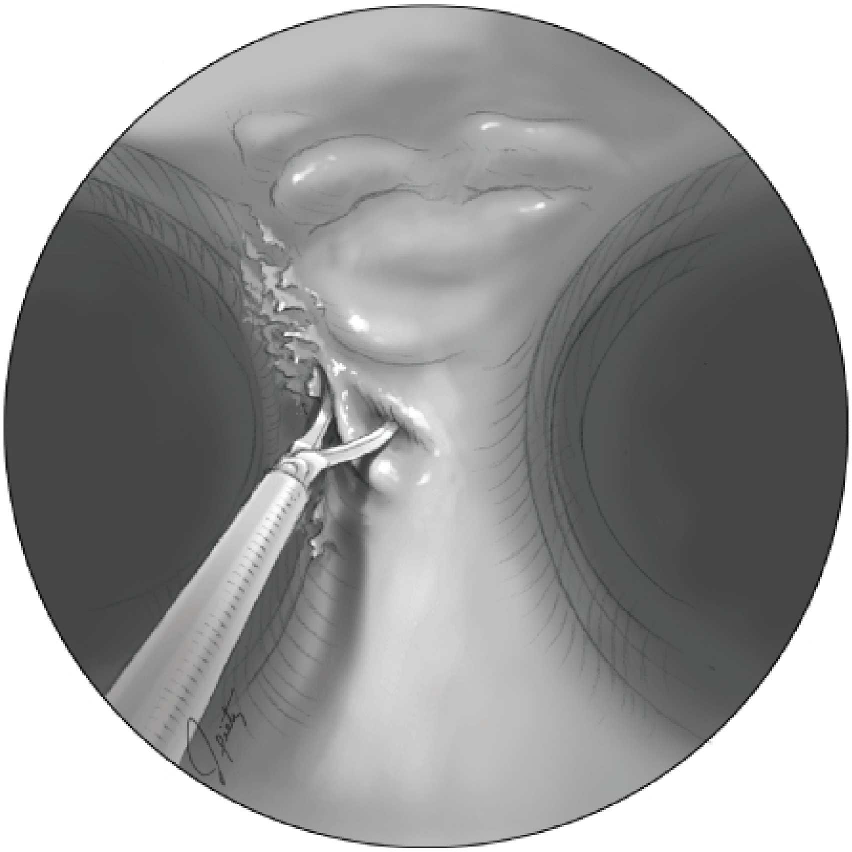
5. **Instrument Insertion.** The distending medium flow is begun, and the operative hysteroscope is inserted into the endocervical canal under direct visualization. On entering the endometrial cavity, a panoramic inspection is performed first to identify the septum.

6. **Septum Incision.** When scissors are used, a surgeon should attempt to keep the line of the incision in the anteroposterior midline. Transection begins caudally, at the septum apex, and continues cephalad toward the fundus. Bites with the scissors are taken bilaterally and are directed toward the horizontal midline (Fig. 41-39.2). During incision of the septum, drifting from the vertical midline is common. Incisions typically drift posteriorly in an anteverted uterus and anteriorly in a retroverted one. Thus, the surgeon may pause and re-orient periodically.

   During septoplasty, incision rather than complete resection of the septum is sufficient. Septal stumps are retracted into the myometrium as the septum is transected.

   In most cases, the septum is relatively avascular, and cutting at its midpoint typically causes little bleeding. As a result, clues that indicate that transection is complete include reaching tissue of increasing vascularity, receiving instruction from the laparoscopist that the hysteroscope is nearing the uterine serosa, and reaching a level in line with the tubal ostia.

FIGURE 41-39.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Septum incision.

7. **Procedure Completion.** After incision, the hysteroscope and tenaculum are removed. Completion of laparoscopy follows the steps outlined in Section 41-28, Laparoscopy.

Postoperative

Recovery following septoplasty is rapid and typically without complication. Light bleeding or spotting may last 1 week or more. Patients may resume normal diet and activities as desired.

To stimulate endometrial proliferation and prevent adhesion reformation, oral estrogen administration has proved effective. Although several regimens can be used, we prescribe 2 mg estradiol orally for 30 days.

Attempts at conception should be delayed for 2 to 3 months following surgery. If septum resection appeared incomplete at the time of surgery, or if recurrent miscarriage or amenorrhea develops, then postoperative HSG or a second hysteroscopy should be performed. Complete removal of the septum or adhesiolysis may be required (see Section 41-41, Lysis of Intrauterine Adhesions).

With subsequent pregnancy, if the myometrium was not entered, cesarean delivery is required only for obstetric indications.

41-40 HYSTEROSCOPIC PROXIMAL FALLOPIAN TUBE CANNULATION

Proximal fallopian obstruction may result from pelvic inflammatory disease (PID), intratubal dÃ©bris, congenital malformations,

tubal spasm, endometriosis, tubal polyps, and salpingitis isthmica nodosa (SIN). Therapeutic approaches to occlusion in this portion of the tube include tubal cannulation, surgical tubocornual anastomosis, and in vitro fertilization (IVF) (Kodaman, 2004).

Proximal fallopian tube cannulation may be performed as an outpatient radiologic procedure using fluoroscopy (Papaioannou, 2003). Alternatively, cannula placement may be completed with hysteroscopic guidance (Confino, 2003). If a hysteroscopic approach is selected, laparoscopy typically is used concurrently. This allows evaluation and treatment of both proximal and distal tubal disease.

During cannulation, attempts are made to flush out dÃ©bris from within the tubes and perform chromotubation.

Preoperative

PATIENT EVALUATION

Proximal tubal occlusion typically is identified with hysterosalpingography (HSG) during evaluation of female infertility, and this modality is described in Chapters 2, Hysterosalpingography and 19, Hysterosalpingography.

To avoid disruption of an early pregnancy, preoperative beta human chorionic gonadotropin β-hCG testing is warranted in most patients. Although this procedure may be performed at any time during the menstrual cycle, the early proliferative phase offers the advantage of a thinner endometrium to allow easy identification of tubal ostia.

CONSENT

In addition to general complications associated with hysteroscopy and laparoscopy, patients undergoing proximal tubal cannulation should be informed of the small risk of tubal perforation. Fortunately, because the guidewire measures only 0.5 mm in diameter, tubal damage is rarely significant and can be assessed by concurrent laparoscopic examination of the perforated tube.

In most cases, women with both proximal and distal tubal disease are best managed with IVF. As discussed in Chapter 9, Hydrosalpinx, hydrosalpinges, when present, can lower IVF success rates. Thus, consideration of and consent for salpingectomy should accompany plans for proximal tubal cannulation.

PATIENT PREPARATION

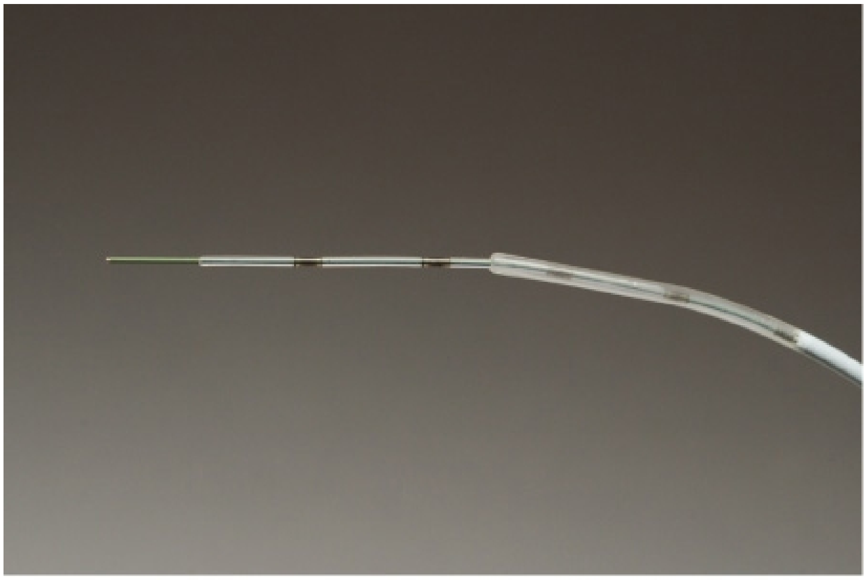
The risk of pelvic infection is low. However, because adhesions following such infection can have damaging effects on fallopian tube health, patients should receive either a first- or second-generation cephalosporin prior to surgery. In addition, laminaria tents or misoprostol may be used to aid in hysteroscope insertion (see Section 41-35, Hysteroscopy).

Intraoperative

INSTRUMENTS

Fallopian tubes may be cannulated with a catheter system such as the one displayed in Figure 41-40.1. This system contains an outer cannula, an inner cannula, and an inner guidewire. The preset bend of the outer cannula aids placement of both the inner cannula and guidewire into the tubal ostium. Once the inner cannula has been threaded into the proximal fallopian tube, the guidewire is removed. The inner cannula, now emptied of the guidewire, can be use to flush dÃ©bris from the fallopian tube and allow chromotubation (see Chap. 19, Laparoscopy).

FIGURE 41-40.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Photograph of hysteroscopic tubal cannulation catheter.

Surgical Steps

1. **Anesthesia and Patient Positioning.** Hysteroscopic tubal cannulation with concurrent laparoscopy typically is an outpatient procedure performed under general anesthesia. The patient is placed in dorsal lithotomy position, the abdomen and vagina are surgically prepared, and a Foley catheter is placed.

2. **Medium Selection.** No electrosurgery is required for tubal cannulation; thus saline is the preferred medium (see Section 41-35, Hysteroscopy).

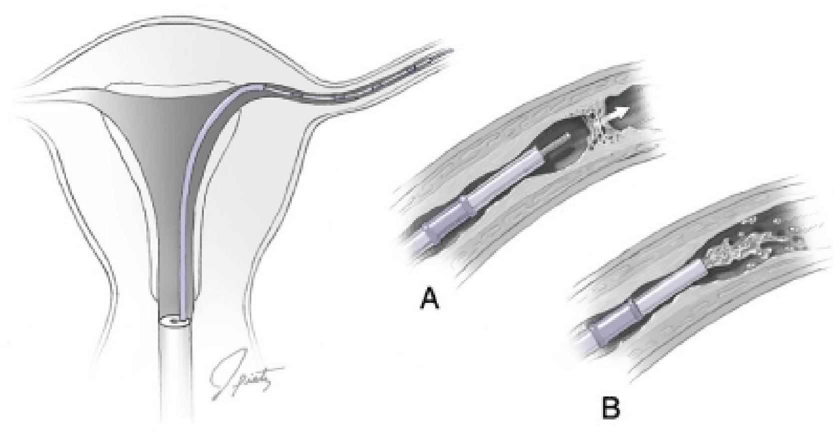
3. **Laparoscopy.** The laparoscope is inserted as described in Section 41-28, Laparoscopy.

4. **Cervical Dilatation.** Because a smaller-diameter operative hysteroscope is required for tubal cannulation, cervical dilatation may not be required. If needed, it is performed as described in Section 41-16, Sharp Dilatation and Curettage.

5. **Hysteroscope Insertion.** The flow of saline is begun, and the hysteroscope is inserted. A panoramic inspection of the entire cavity is performed.

6. **Tubal Cannulation.** The catheter system is threaded through an operating port of the hysteroscope. Under direct visual guidance, the outer catheter is advanced and placed at one of the tubal ostia. The inner catheter then is threaded approximately 2 cm into the proximal fallopian tube (Fig. 41-40.2). The guidewire is removed.

FIGURE 41-40.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Tubal cannulation.

7. **Tubal Flushing.** The inner catheter is flushed with water-soluble dye. The laparoscope should be positioned to allow inspection of the distal tube to note the presence or absence of dye spill.

8. **Concurrent Procedures.** If distal tubal adhesions are noted, laparoscopic lysis of adhesions may be performed concurrently.

9. **Procedure Completion.** Following cannulation, the hysteroscope and cervical tenaculum are removed. Laparoscopy is completed as described in Section 41-28, Laparoscopy.

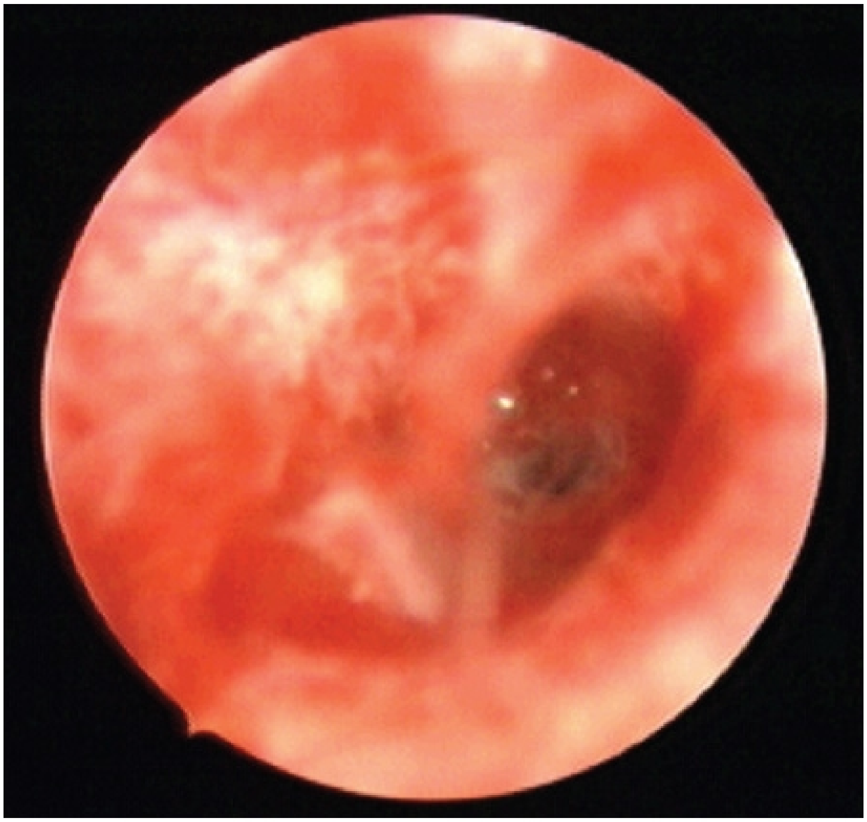
Postoperative

Recovery from hysteroscopic tubal cannulation and laparoscopy typically is quick and uncomplicated. Patients may resume diet, activity, and attempts at conception as desired.

41-41 LYSIS OF INTRAUTERINE ADHESIONS

Intrauterine adhesions, also called *synechiae,* may develop following uterine curettage. Less commonly, they may result from pelvic irradiation or tuberculous endometritis. The presence of these adhesions, also termed Asherman syndrome, may lead to hypo- or amenorrhea and infertility or pregnancy loss in women (Fig. 41-41.1).

FIGURE 41-41.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Hysteroscopic photograph of intrauterine adhesions. (Courtesy of Dr. Kevin Doody.)

Treatment goals include surgical recreation of normal intrauterine anatomy and prevention of adhesion re-formation. Surgery involves hysteroscopic transection rather than excision of adhesions. Thus, thin adhesions usually can be lysed using only blunt force from the hysteroscopic sheath. Dense adhesions, however, usually require hysteroscopic division with scissors or laser tip.

Postoperative pregnancy and live delivery rates are markers of surgical success. These rates vary depending on the thickness of adhesions and the degree of cavity obliteration. For this reason, various adhesion classification systems are useful to help predict the success of adhesiolysis for a given woman (Al-Inany, 2001).

Preoperative

PATIENT EVALUATION

Although hysteroscopy and saline-infusion sonography (SIS) both can identify adhesions accurately, hysterosalpingography (HSG) is preferred initially because it allows concurrent assessment of tubal patency. However, after adhesions have been noted, diagnostic hysteroscopy is recommended to assess the thickness and density of these bands (Fayez, 1987).

Additionally, completion of fertility assessment, including semen analysis and assessment of ovulation, is recommended prior to surgery to help predict the chances of conception following the procedure.

CONSENT

In general, hysteroscopic adhesiolysis is an effective tool to correct menstrual disorders and improve fertility in women with uterine adhesions (Valle, 2003; see also Chap 18, Diagnosis and Treatment). Although overall cumulative delivery rates in those with no

other fertility factors ranges from 60 to 70 percent, lower rates generally are associated with more severe disease (Pabuccu, 1997; Zikopoulos, 2004). In addition, pregnancies following surgery may be complicated by placenta accreta or increta or by preterm labor (Dmowski, 1969).

The complications of intrauterine adhesiolysis mirror those for operative hysteroscopy. However, the risk of uterine perforation may be increased. For this reason, patients also should be consented for diagnostic laparoscopy.

PATIENT PREPARATION

As with most operative hysteroscopic procedures, antibiotic prophylaxis is warranted. A and a first- or second-generation cephalosporin or other suitable antibiotic is appropriate. Additionally, laminaria tents or misoprostol may be used preoperatively to ease cervical dilatation (see Section 41-35, Hysteroscopy).

Intraoperative

Surgical Steps

1. **Anesthesia and Patient Positioning.** Hysteroscopic lysis of adhesions typically is a day-surgery procedure performed under general anesthesia. The woman is placed in dorsal lithotomy position, the vaginal is surgically prepared, and a Foley catheter is inserted.

2. **Medium Selection.** The choice of distending medium is dictated by the tool used. Sharp transection with scissors, neodymium:yttrium-aluminum-garnet (Nd:YAG) laser, or bipolar instrument can be performed in any liquid medium. However, thick adhesions often require resection rather than division, and they are severed close to the myometrium. Thus, the potential for creation of large denuded areas and fluid intravasation is great. Accordingly, for many surgeons, 0.9-percent saline is preferred because hyponatremia is avoided if fluid overload does develop (see Section 41-35, Hysteroscopy).

3. **Concurrent Laparoscopy.** Because of the increased risk of uterine perforation in those with more severe obliteration of the cavity, adjunctive laparoscopy may guide surgeons as to instrument proximity to the uterine serosa. The decision to use a laparoscope is individualized, and its placement follows the steps described in Section 41-28, Laparoscopy.

4. **Cervical dilatation.** Using a Pratt or other suitable dilators, the surgeon dilates the cervix as described in Section 41-16, Sharp Dilatation and Curettage.

5. **Instrument Insertion.** The distending medium flow is begun, and the operative hysteroscope is inserted into the endocervical canal under direct visualization. On entering the endometrial cavity, a panoramic inspection is performed first to identify adhesions.

6. **Approach to Lysis.** In general, a systematic approach to adhesiolysis begins with either blunt or sharp disruption of the most central adhesions and moves gradually to reach the most lateral. The size and qualities of adhesions may vary. Thin endometrial adhesions usually can be disrupted with blunt force from the hysteroscopic sheath alone. More commonly, myofibrous and fibrous adhesions are denser and may require complete resection.

   Adhesiolysis is continued until the endometrial cavity is restored to normal size and contour, and the tubal ostia are seen. Importantly, procedures may require termination prior to this if significant fluid volume deficits are reached (see Section 41-35, Hysteroscopy).

7. **Chromotubation.** At completion of adhesiolysis, transcervical chromotubation is performed to document tubal patency.

8. **Mechanical Uterine Distention.** Mechanical endometrial cavity distention has been used to prevent treated areas from adhering following surgery. Either an intrauterine device (IUD), placed for 3 months, or an 8F pediatric Foley catheter balloon, used for 10 days, may be chosen. In comparison of the two, Orhue and colleagues (2003) noted fewer new adhesions and greater pregnancy rates in woman using the balloon. If a Foley balloon is placed, antibiotic prophylaxis with either doxycycline 100 mg orally twice daily or other appropriate antibiotic is recommended during balloon use.

Postoperative

Recovery from hysteroscopic resection is rapid and typically without complication. Patients may resume normal activities and diet as tolerated.

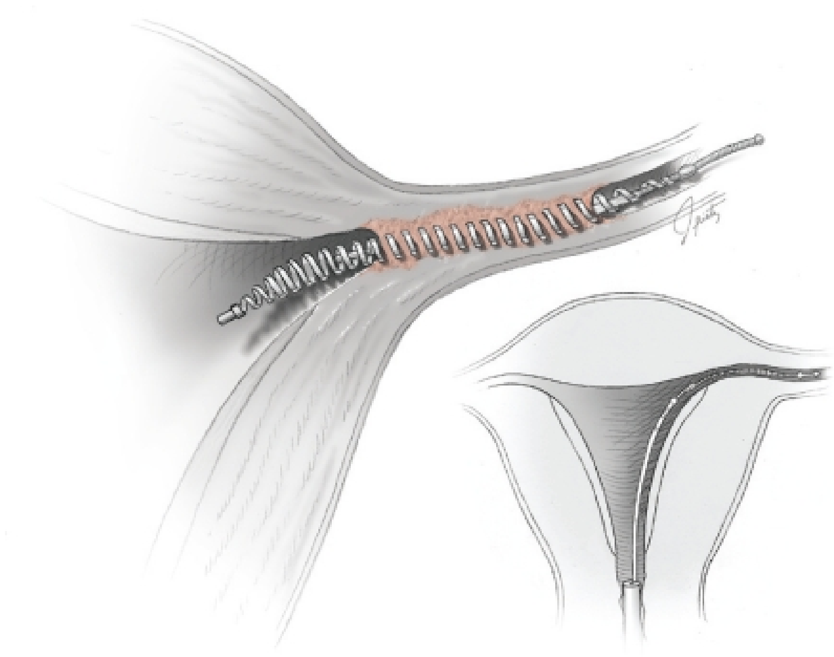
To stimulate endometrial proliferation and prevent adhesion re-formation, oral estrogen administration has proved effective. Although several regimens can be used, we prescribe 2 mg of estradiol orally for 30 days following adhesiolysis.

New adhesions can form following adhesiolysis. In their early stages, these bands are thinner and thus more amenable to successful resection. For this reason, another hysteroscopy or HSG typically is performed at 3 months following the initial resection. If significant new adhesions are found, a repeat surgical lysis of adhesions is planned. To allow adequate uterine healing, attempts at pregnancy by the patient should be delayed for 2 to 3 months.

41-42 HYSTEROSCOPIC PLACEMENT OF ESSURE MICROINSERTS

Hysteroscopic placement of the Essure Permanent Birth Control System (Conceptus, Inc., San Carlos, CA) is a transcervical method of female sterilization. With this procedure, a coil device, termed a microinsert, is inserted into the lumen of proximal section of each fallopian tube. Once in place and released from its delivery catheter, the microinsert expands and anchors itself in the fallopian tube (Fig. 41-42.1). Over time, synthetic fibers within the microinsert incite a chronic inflammatory response and local tissue ingrowth from the surrounding tube. This ingrowth leads to complete tubal lumen occlusion, which is documented by hysterosalpingography (HSG) at 3 months following surgery.

FIGURE 41-42.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Microinsert placement and ingrowth of tissue.

As with any permanent birth control method, candidates should be confident in their decision for sterilization. Contraindications include pregnancy or pregnancy termination within the prior 6 weeks, recent pelvic infection, known tubal occlusion, and allergy to nickel or radiographic contrast media.

Preoperative

PATIENT EVALUATION

Pregnancy should be excluded prior to sterilization using a serum or urine beta human chorionic gonadotropin β-hCG test.

CONSENT

For many women, the Essure System is a safe and effective method of birth control, with efficacy rates comparable with current laparoscopic sterilization rates (Magos, 2004). However, microinsert placement may not be possible in all women due to tubal ostium stenosis or spasm or an inability to visualize the ostia (Cooper, 2003). Rates of successful placement average 88 to 95 percent (Kerin, 2003; Ubeda, 2004).

In general, complications of Essure System placement are similar to those of hysteroscopy. However, rates of fluid volume overload are low because in most cases procedure lengths are short (15 to 30 minutes), and opening of endometrial vascular channels is minimal. Uterine or tubal perforation has been noted. Rates approximate 1 to 2 percent and in most cases are clinically insignificant (Kerin, 2003; Cooper, 2003).

PATIENT PREPARATION

Because menstrual bleeding and a thick endometrium can impair identification of tubal ostia, this procedure typically is performed during the early proliferative phase of the menstrual cycle. This also decreases the chance of an unidentified luteal phase pregnancy.

Preoperative analgesia may be considered and typically consists of a nonsteroidal anti-inflammatory drug given 30 to 60 minutes before the procedure.

Intraoperative

INSTRUMENTS

The Essure System is disposable and contains a handle, delivery catheter, release catheter, delivery wire, and microinserts. Each microinsert is attached to the end of a delivery wire, which is housed within a release catheter. In turn, the release catheter is surrounded by a delivery catheter.

Surgical Steps

1. **Anesthesia and Patient Positioning.** Hysteroscopic placement of the Essure System can be performed in an outpatient setting under local analgesia with or without intravenous sedation. Alternatively, a day-surgery setting using general anesthesia may be selected. The patient is placed in dorsal lithotomy position, and the vagina is surgically prepared.

2. **Media Selection.** Electrosurgery is not required, and therefore, 0.9-percent saline is used commonly to avoid the increased expense and risk of hyponatremia associated with nonelectrolyte solutions. As with any hysteroscopic procedure, accurate calculation of fluid volume deficits during the procedure is essential (see Section 41-35, Hysteroscopy).

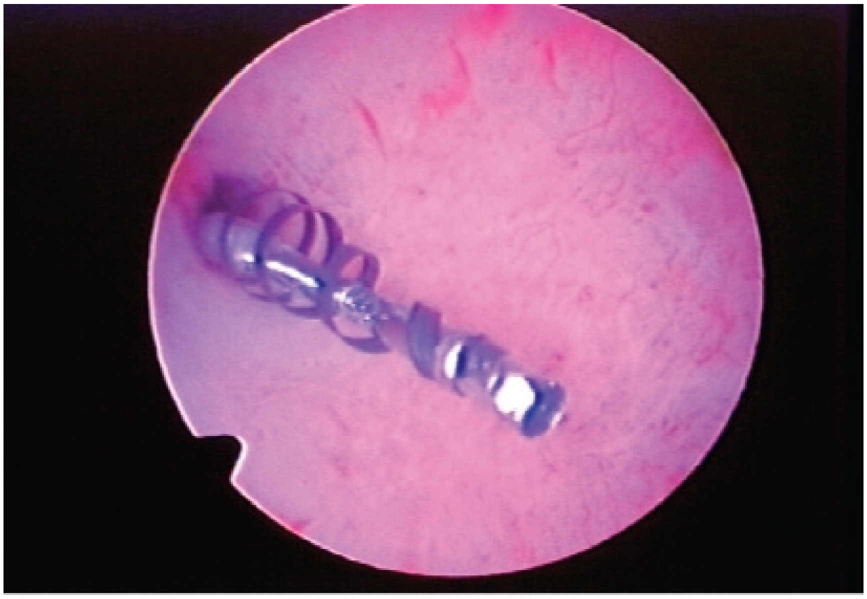
3. **Hysteroscope Insertion.** Vaginal retractors or a speculum provides access to the cervix, and a tenaculum may be used for adequate cervical traction to insert the hysteroscope. Depending on the diameter of the operative hysteroscope, cervical dilatation may or may not be required, as described in Section 41-16, Sharp Dilatation and Curettage. A 12- to 30-degree hysteroscope is preferred to provide easily visualization of the cornua, and a 5F operating channel is required.

4. **Ostia Identification.** Requisite for completion of the procedure, both tubal ostia must be visualized.

5. **Microinsert Delivery.** The outermost catheter of the system, the delivery catheter, is threaded through the operating channel of the hysteroscope. Its tip is inserted into one tubal ostium. The delivery catheter is retracted into the Essure System handle, and an inner cannula, the release catheter, is seen. Next, as the release catheter is retracted, the microinsert begins to uncoil. Ideally, four to eight coils of the microinsert trail into the endometrial cavity (Fig. 41-42.2). As a final step, a guidewire that is attached to the distal end of the microinsert is detached and retracted.

   These steps are repeated at the opposite ostium.

FIGURE 41-42.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

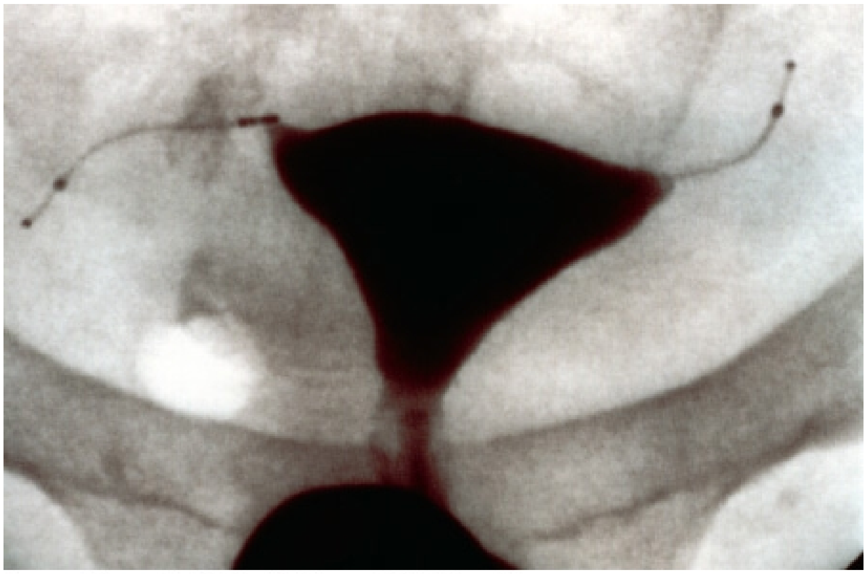
Hysteroscopic photograph of Essure microinsert coils within the tubal ostium. (Courtesy of Conceptus, Inc.)

Postoperative

Patients typically resume normal diet and activity within the first 24 hours following surgery. Cramping is common within the first few days, and light spotting or bleeding may be noted during the week following surgery.

To document complete tubal occlusion, HSG is performed at 3 months following insertion (Fig. 41-42.3). Until this time, an alternative method of contraception should be used. Rarely, in those with correct placement, tubal occlusion may not be complete at 3 months, and a second HSG at 6 months may be required to document sterilization.

FIGURE 41-42.3



Hysterosalpingography displaying correct Essure microinsert placement. (Courtesy of Conceptus, Inc.).

In addition, microinserts can be expelled. Thus, if no device is identified, or if 18 or more coils are seen trailing into the uterine cavity during HSG, then the microinsert should be replaced or alternative method of contraception used (Magos, 2004).

Essure microinserts can conduct electrical energy. Therefore, it is recommended that direct visualization of the inserts or the cornual area be obtain hysteroscopically or laparoscopically prior to any subsequent electrosurgical procedures near the inserts.

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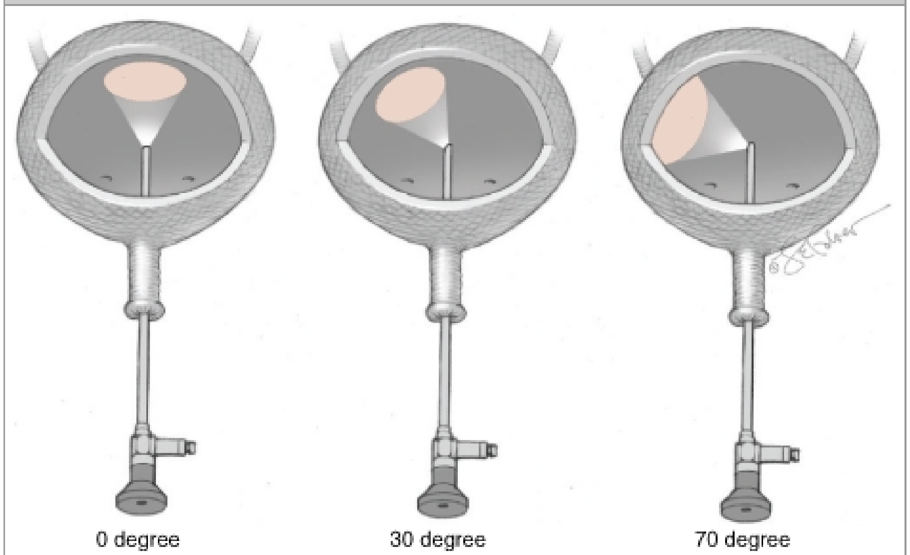
42-1 DIAGNOSTIC AND OPERATIVE CYSTOSCOPY AND URETHROSCOPY

The lower urinary tract may be injured during gynecologic surgery. Therefore, diagnostic cystoscopic evaluation typically is warranted following procedures in which the bladder and ureters have been placed at risk. Operative cystoscopy is within the scope of many gynecologists for the passage of ureteral stents, lesion biopsy, and foreign-body removal. Of these, ureteral stenting may be indicated to assess ureteral patency following gynecologic surgery or to delineate the ureter's course in patients with abnormal pelvic anatomy.

Rigid and flexible cystoscopes are available, although in gynecology a rigid scope typically is used. A cystoscope is composed of a sheath, bridge, telescope, and obturator. The sheath contains a port for fluid infusion and a second port for fluid egress. For office cystoscopy, a sheath measuring 17F affords greater comfort, whereas for operative cases, a 21F or wider-diameter cystoscope is preferred to allow rapid infusion of fluids. The sheath's end is sharp, and in patients in whom the urethral meatus is narrow, an obturator is placed inside the sheath and serves to introduce it smoothly. The bridge attaches to the proximal sheath and allows coupling between the telescope and sheath.

Several viewing angles are available and include 0-, 30-, and 70-degree optical views (Fig. 42-1.1). The 0-degree telescopes are used for urethroscopy. For cystoscopy, a 70-degree telescope is superior in providing the most comprehensive view of the lateral, anterior, and posterior walls; trigone; and ureteral orifices. To achieve a comparable view, a 30-degree scope requires additional manipulation. However, a 30-degree scope does offer advantages and allows surgeons greater flexibility because it can be used for either urethroscopy or cystoscopy during a given case. For operative cystoscopic cases in which instrument are passed down the sheath, a 30-degree scope must be used because with 0- and 70-degree scopes, operative instruments lie outside the field of view.

FIGURE 42-1.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Cystoscopic optical views.

Preoperative

PATIENT EVALUATION

A significant incidence of bacteruria follows cystoscopy. Thus, prior to cystoscopy, urinary tract infection should be excluded.

CONSENT

If performed properly, complications of diagnostic cystoscopy are rare. Of these, infection is the most common.

PATIENT PREPARATION

Although evidence-based data are lacking for its use, oral antibiotic prophylaxis is commonly given postoperatively.

Intraoperative

Surgical Steps

1. **Distention Media.** The bladder must be distended adequately to fully visualization all surfaces, and for diagnostic purposes, saline or sterile water may be used. To ensure adequate medium flow, an infusion bag should be elevated significantly above the level of the symphysis. The volume needed may vary but is reached when bladder walls are not collapsing inward. Care must taken to avoid overdistending the bladder, which may result in temporary urinary retention. If the bladder is distended beyond its capacity, excess fluid will leak out the urethral meatus and around the scope rather than resulting in bladder rupture, which is rare.

2. **Indigo Carmine.** If intraoperative cystoscopy is performed to document ureteral patency Â½ to 1 ampule of indigo carmine is administered prior to the procedure.

3. **Anesthesia and Patient Positioning.** Cystoscopy may be performed in any lithotomy position with the legs positioned in stirrups. For office cystoscopy, 2-percent lidocaine jelly is instilled into the urethra 5 to 10 minutes prior to cystoscope insertion. For operative procedures, an additional 50 mL of 4-percent lidocaine solution is instilled into the bladder. The perineum and urethral meatus are surgically prepared.

4. **Cystoscopy.** The anterior urethral wall is very sensitive, and the sharp bevel edge, if directed anteriorly, may cause increased discomfort. Therefore, a cystoscope is inserted into the urethral meatus with the bevel directed posteriorly. Immediately following insertion into the meatus, media flow is started. The cystoscope is advanced to the bladder under direct visualization.

5. **Bladder Inspection.** On entry into the bladder, the cystoscope is withdrawn slowly until the bladder neck is identified. The cystoscope then is advanced and rotated 180 degrees. An air bubble is noted at the dome, which provides orientation for the remainder of the cystoscopic examination. The cystoscope then is withdrawn to the bladder neck and angled downward to provide a view of the trigone and both ureteral orifices. If ureteral patency is the topic of focus, brisk flow of indigo carmine should be seen from each orifice. Peristalsis of the ureteral orifice alone, without flow, is insufficient to document patency. Moreover, scant flow may indicate partial ureteral obstruction. Bladder walls are inspected by rotating the cystoscope until all surfaces have been evaluated. During inspection, digital elevation of the anterior vaginal wall is beneficial if pelvic organ prolapse is present.

6. **Operative Cystoscopy.** The operative instrument (biopsy or grasping forceps or scissors) is introduced through the operative port until viewed at the end of the cystoscope. Prior to instrument insertion, a rubber adapter cap is positioned over the operative port to create a watertight seal with the operative instrument. Once in view, the instrument and cystoscope are moved together as a unit toward the area of interest.

7. **Ureteral Stenting.** Ureteral stents may be placed at several junctures during surgery. They may be placed at the beginning of surgery and left through its duration to define anatomy in patients in whom the ureter is at surgical risk of injury. Alternatively, they may be placed intraoperatively to exclude ureteral injury. Finally, ureteral stents may be positioned and

left in place at the conclusion of surgery if ureteral injury is suspected or identified. Duration of postoperative stenting is variable and based on clinical indications.

Ureteral stents are available in a variety of sizes, and those ranging from 5F to 7F are used commonly. Stents vary in length from 12 to 30 cm, and a 24-cm length is appropriate for most adults. Generally, open-ended or whistle-tip stents are used to delineate anatomy in patients in whom the ureter is at surgical risk or to exclude obstruction. Double- or single-pigtail stents are used in situations in which prolonged ureteral drainage is required.

8. **To Exclude Ureteral Obstruction.** An open-ended or whistle-tip stent is threaded through the operative channel of a 30-degree cystoscope and into the field of view. By advancing both the stent and cystoscope toward the orifice, the stent is passed into the ureteral orifice. After the stent has entered the orifice, it is threaded and advanced manually. Alternatively, an AlberrÃin bridge may be used. This specialized bridging sheath allows deflection and guidance of a stent into an orifice. Once a stent is placed within the orifice, it is advanced past the level of suspected obstruction. If a stent is advanced easily, obstruction is excluded. In most gynecologic surgeries, this would not be higher than the pelvic brim. When passing a stent, undue pressure is avoided during advancement to avoid ureteral perforation.

9. **To Delineate Anatomy.** For this purpose, the stent is advanced until resistance is met, which indicates that the renal pelvis has been reached. The stent is tied securely to the transurethral catheter and drains into the Foley bag. At the conclusion of surgery, the stent is removed.

10. **Ureteral Stenting.** In patients in whom a ureteral stent is required postoperatively, a double-pigtail type stent is used. The proximal and distal coils of this stent prevent renal pelvis injury and secure placement in the bladder, respectively.

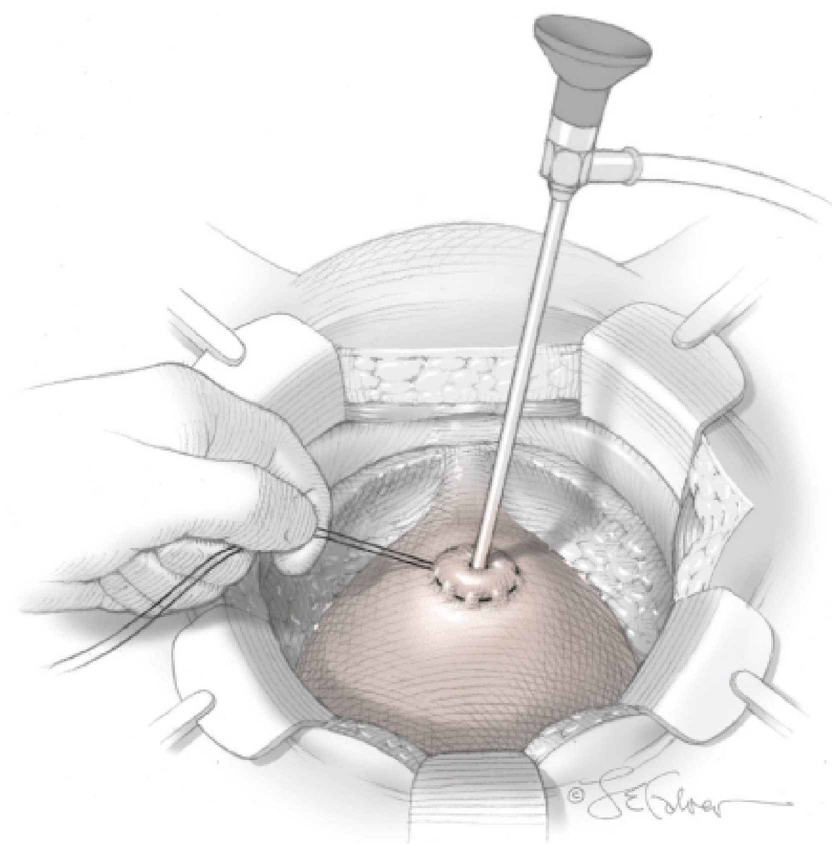
    A guidewire is first threaded into the ureteral orifice and passed to the renal pelvis. The pigtail stent then is placed over the guidewire and advanced by a pusher device until the distal end enters the bladder. The guidewire is removed, allowing the ends to coil in the renal pelvis and bladder, respectively.

11. **Biopsy.** Mucosal lesions can be biopsed with a minimal amount of risk and discomfort to the patient. A biopsy instrument is introduced into the cystoscope's operative port and brought into the operative field. With the instrument directly in the field of view, the cystoscope is moved directly to the lesion. Biopsy is performed, and the cystoscope and instrument are withdrawn through the urethra together. In this way, a biopsy specimen is not pulled through the sheath and possibly lost. Bleeding usually is minor and will stop by itself. For brisk bleeding, electrosurgical coagulation can be used if a nonconducting solution was selected as the distention medium.

12. **Removal of Foreign Bodies.** Foreign bodies, such as stones, are removed using the same technique as biopsy. The instrument is used to grasp the foreign body and then is removed together with the cystoscope.

13. **Suprapubic Teloscopy.** Suprapubic teloscopy is a technique used to visualize the bladder through an abdominal approach. We have found this technique to be valuable when the ureters must be assessed during a difficult cesarean delivery or during a laparotomy in which a woman has not been positioned to allow easy cystoscopic access to the urethra. The bladder is distended using the transurethral Foley catheter until the bladder wall is tense. A wide purse-string using 2-0 absorbable suture then is placed at the bladder dome, taking deep bites into the bladder muscularis (Fig. 42-1.2). The two suture ends are elevated but held loosely. A small stab incision then is made in the purse-string's center, and a cystoscope is introduced into the bladder. For suprapubic teloscopy, a 30-degree cystoscope is most effective. The two suture ends then are pulled up and held tightly to prevent escape of the distending fluid. To allow visualization of the trigone and ureteral orifices, the Foley bulb is deflated but left in place. Indigo carmine is given if necessary to document ureteral efflux. If the ureteral orifices still cannot be visualized, the bladder incision is extended to allow direct visualization. At the conclusion of the teloscopy, the cystoscope is removed, and the purse-string suture is tied, closing the cystotomy.

FIGURE 42-1.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Suprapubic teloscopy.

Postoperative

Office cystoscopy does not require specific postoperative management except for prophylactic antibiotics. With operative cystoscopy, hematuria may develop, generally clears within a few days, and is considered significant only if associated with symptomatic anemia. With long-term ureteral stenting, additional complications may include ureteral spasm, which typically presents as back pain.

42-2 BURCH COLPOSUSPENSION

Abdominal-approach anti-incontinence procedures attempt to correct stress urinary incontinence (SUI) by stabilizing the anterior vaginal wall and urethrovesical junction in a retropubic location. Specifically, the Burch procedure, also known as retropubic urethropexy, uses the strength of the iliopectineal ligament (Cooper ligament) to stabilize the anterior vaginal wall and anchor it to the musculoskeletal framework of the pelvis (see Fig. 38-25).

The Burch colposuspension usually is performed through a Pfannenstiel or Cherney incision (see Section 41-2, Pfannenstiel Incision). More recently, however, some surgeons have introduced laparoscopic approaches that use suture or mesh to affix the paravaginal tissues to Cooper ligament (Ankardal, 2004; Zullo, 2004). However, compared with open Burch colposuspension, laparoscopic approaches have proved less effective (el Toukhy, 2001; Moehrer, 2002).

Preoperative

PATIENT EVALUATION

Prior to surgery, patients undergo complete urogynecologic evaluation. Urodynamic testing is recommended to differentiate stress and urge incontinence as well as to assess bladder capacity and voiding patterns (see Chap. 23, Diagnostic Testing).

Many women with SUI also may have associated pelvic organ prolapse. For this reason, other indicated pelvic reconstructive surgeries commonly accompany Burch colposuspension.

In women requiring hysterectomy, hysterectomy does not appear to improve or worsen success rates of Burch colposuspension (Bai, 2004; Meltomaa, 2001). Hysterectomy in this setting may be performed either vaginally or abdominally without significant differences in perioperative complications (Sze, 1997).

CONSENT

For most women with SUI, Burch colposuspension offers a safe, effective long-term treatment for incontinence. Success rates vary based on how success is defined, but it is generally believed that this operation provides symptomatic cure in approximately 85 percent of patients. Surgical risks compare similarly with other surgeries for SUI (Green, 2005; Lapitan, 2003). Intraoperative complications are rare and may include ureteral injury, bladder perforation, and hemorrhage (Galloway, 1987; Ladwig, 2004).

Complications, however, are not uncommon postoperatively and may include urinary tract or wound infection, voiding dysfunction, de novo urinary urgency, and pelvic organ prolapse, primarily enterocele formation (Alcalay, 1995; Demirci, 2000, 2001; Norton, 2006). Overcorrection of the urethrovesical angle has been suggested as a cause of these long-term urinary and prolapse complications.

Antibiotic Prophylaxis

Prior to Burch colposuspension, administration of antibiotics preoperatively is warranted. Bhatia (1989) showed significantly less febrile morbidity in women given 1-g doses of cefazolin intravenously before, during, and 8 hours after colposuspension compared with women receiving no prophylaxis.

Intraoperative

Surgical Steps

1. **Anesthesia and Patient Positioning.** The patient is placed supine with legs in Allen stirrups (Allen Medical Systems, Acton, MA) in low lithotomy position. The abdomen and vagina are surgically prepared, and a Foley catheter is placed.

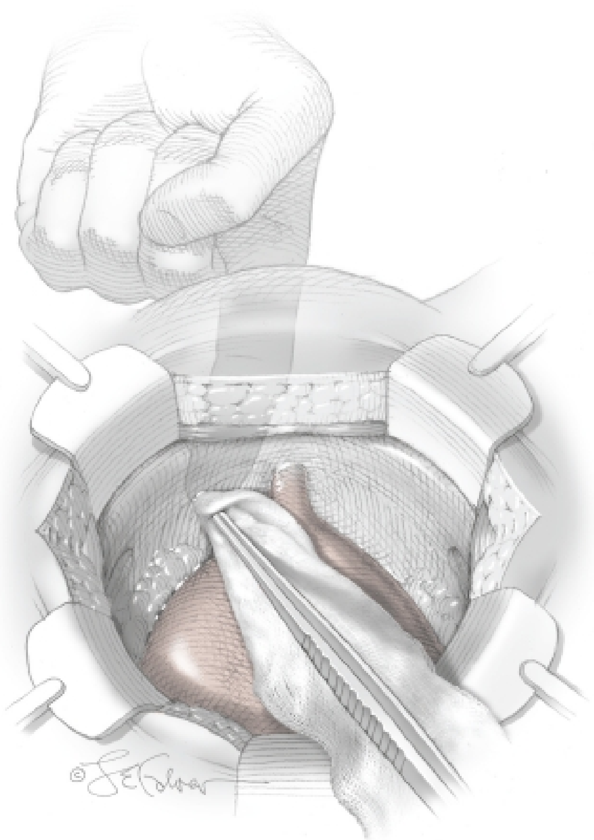
2. **Abdominal Incision.** A low Pfannenstiel or Cherney incision is performed (see Section 41-2, Pfannenstiel Incision). Surgery in the space of Retzius is easier to accomplish if the transverse incision is placed low on the abdomen, approximately 1 cm above the upper border of the pubic symphysis. If hysterectomy, culdoplasty, or other intraperitoneal procedure is planned, the peritoneum is entered and concurrent surgery completed prior to beginning colposuspension.

3. **Entry into the Space of Retzius.** On closure of the peritoneum, the avascular plane between the pubic bone and loose areolar tissue, that is, the space of Retzius, must be exposed. To enter this space, the fingers of one hand gently dissect along the cephalad surface of the pubic bone. Alternatively, gentle sponge dissection can be used to open this space (Fig. 42-2.1). The loose areolar tissue found behind the symphysis will separate easily from the bone. However, if the wrong plane is entered, bleeding can occur. Direct exposure of the back of the pubic bone ensures that the correct space has been entered. The bladder and urethra gently pull downward and away from the pubic bone, and the space of Retzius opens.

   In those with prior surgery, sharp dissection may be required. Dissection begins with the curved tips of the Metzenbaum scissors directly on the pubic bone and progresses dorsally until the space is exposed. Clips and sutures can be used to control bleeding vessels.

   During space of Retzius dissection, the obturator canal should be identified early to avoid neurovascular injury to the obturator vessels and nerves (see Fig. 38-25). The iliopectineal ligament (Cooper ligament) is identified as the space is opened.

FIGURE 42-2.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Entry into the space of Retzius.

4. **Exposing the Anterior Vaginal Wall.** Following creation of this space, the index and middle fingers of the surgeon's nondominant hand are place in the vagina. With one on each side, the finger pads straddle the urethra and push the vagina ventrally. This maneuver alone will clear much of the fat off the anterior vaginal wall.

   If necessary, the surgeon can use a Kitner (peanut) sponge or gauze sponge stick on either side of the urethra to wipe the fatty connective tissue laterally. Upward pressure by the vaginal fingers and downward, lateral pressure during this blunt separation reveal the white glistening anterior vaginal wall. Importantly, to protect the delicate urethral musculature, this dissection should remain lateral to the urethra.

   Dissection may bring laceration of vessels within the Santorini plexus of paravaginal veins and a risk for significant bleeding. This is controlled easily with upward pressure from the vaginal fingers. Identified vessels can be sealed with electrosurgical coagulation, ligation, or placement of vascular clips.

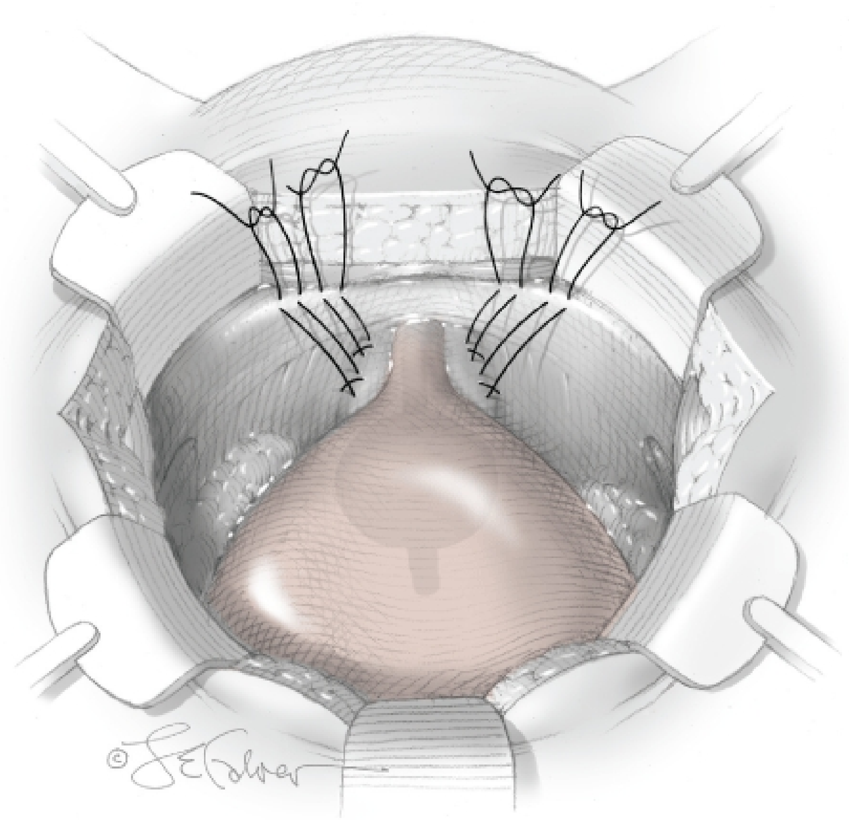
5. **Identifying the Urethrovesical Junction.** The urethrovesical junction is identified to aid correct suture placement. This site can be found by using the surgeon's vaginal hand to position the Foley catheter balloon at the bladder neck. This should be done without pulling the Foley catheter. Tension may drag the bladder into the operative field and increase the risk of suture entry into the bladder.

6. **Suture Placement.** A double-armed 2-0 suture of permanent material is placed laterally on each side of the urethra. The

surgeon's vaginal finger is pressed upward to expose the appropriate area, and the needle point is directed toward that finger. A thimble may be used to avoid needlestick injury. A first suture is placed 2 cm lateral to the urethrovesical junction, and a second suture is placed 2 cm lateral to the proximal third of the urethra. With these stitches, a figure-of-eight suture is used to incorporate a wedge of tissue for support (Fig. 42-2.2). Stitches should incorporate the vaginal muscularis but not the epithelium. Identical sutures are then placed on the opposite side of the urethra.

Both ends of each suture next are placed through the nearest point of the ipsilateral iliopectineal ligament. Slack is removed from each suture, and knots are tied above the ligament. With knot securing, a surgeon invariably creates suture bridges. These should stabilize but not elevate the anterior vaginal wall and urethrovesical junction.

FIGURE 42-2.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Suture placement.

7. **Cystoscopy.** Following suture ligation, Â½ or 1 ampule of indigo carmine is given intravenously. and cystoscopy is performed. This allows identification and removal of any errant sutures that may traverse the bladder mucosa. Moreover, it enables the surgeon to inspect ureteral orifices and document flow as a means to exclude intraoperative ureteral injury.

8. **Catheterization.** At completion of colposuspension, the Foley catheter may remain and drain the bladder. Alternatively, a suprapubic catheter may be placed. In studies, investigators have compared the two and found no differences in incontinence procedure success rates, length of hospitalization, or rates of infection. Urethral catheterization, however, was linked with a shorter duration of catheterization but also greater patient discomfort (Dunn, 2005; Theofrastous, 2002).

9. **Incision Closure.** The abdominal wall fascia is closed in a running fashion with 0-gauge delayed-absorbable suture. The skin is closed using a running subcuticular suture with 4-0 delayed-absorbable material or other suitable skin closure method (see Chap 40, Subcuticular Suturing).

POSTOPERATIVE

In general, recovery follows that associated with laparotomy and varies depending on concurrent surgeries and incision size. A voiding trial as described in Chapter 39, Voiding Trials is performed prior to hospital discharge.

42-3 TENSION-FREE VAGINAL TAPE

The tension-free vaginal tape procedure (TVT) is the most commonly performed operation worldwide for stress urinary incontinence. The procedure is one of the most widely studied anti-incontinence operations, and 5-year cure rates approximate 85 percent. The TVT procedure also has become the prototype for a host of other anti-incontinence operations (SPARC Sling System, American Medical Systems, TOT [transobturator tape], TVT-O [tension-free vaginal tape]). These are all based on the concept that midurethral support is vital to continence.

Tension-free vaginal tape placement is indicated for stress urinary incontinence (SUI) secondary to urethral hypermobility or intrinsic sphincteric deficiency (see Chap 23, Midurethral Slings). It is used for primary cases as well as for those who have had prior anti-incontinence procedures.

During TVT, a permanent sling material is placed underneath the midurethra and brought behind the pubic bone and through the space of Retzius and anterior abdominal wall. The TVT needle is placed blindly through the space of Retzius, and significant bleeding is a risk. A modification of the TVT, the TOT (see Section 42-4, Transobturator Tape Sling) was developed to avoid hemorrhage in this space. However, TVT remains the primary standard operation for SUI.

The TVT device consists of a permanent polypropylene mesh covered with a plastic sheath that is removed after the mesh is placed. The plastic sheath is believed to prevent bacterial contamination of the mesh as it passes through the vagina and to protect the mesh from being damaged during passage. Each end of the mesh is attached to a disposable metal needle that is connected to a reusable metal introducer during placement. A metal catheter guide is used to displace the urethra away from the needle during the procedure.

Preoperative

PATIENT EVALUATION

Prior to performing a TVT procedure, a diagnosis of SUI must be made. A woman should have bothersome symptoms of urine leakage with cough, sneeze, activity, or increased intra-abdominal pressure. A urodynamic evaluation should be performed, and leakage with increases in intra-abdominal pressure in the absence of detrusor contractions should be documented (see Chap. 23, Pressure Flowmetry). In some women, symptoms do not correlate with objective findings of urine loss with stress. For these individuals, a surgical procedure should not be performed. Stress urinary incontinence may not be present, and surgery may fail to improve or may aggravate symptoms. An exception might be a woman with pelvic organ prolapse that is obstructing the urethra. In these women, the prolapse should be replaced during urodynamic testing to attempt to document latent or potential stress incontinence.

CONSENT

Postoperatively, consent process for TVT should include an honest discussion of outcomes. At best, the 5-year cure rate is 85 percent, with another 10 percent significantly improved. However, some patients will develop postoperative urge incontinence, and others will develop bothersome voiding dysfunction. Additionally, with time and aging, incontinence may recur secondary to factors not related to urethral support.

Intraoperative complications include hemorrhage, bladder perforation, and bowel injury. Major vessels are injured in less than 1 percent of patients.

Postoperatively, short-term complications of the procedure include incomplete bladder emptying requiring drainage with a Foley catheter or intermittent self-catheterization for several days. A small percentage of patients will develop long-term urinary retention requiring reoperation for excision or removal of the tape (see Section 42-8, Midurethral Sling Release). In patients who require excision or removal of a piece of the tape, continence rates decrease. The TVT procedure is associated with a learning curve, and urinary retention rates decrease as the number of cases a physician performs increases. Following surgery, vaginal mesh erosion may develop as an early or late complication. This is managed by simple excision of the eroding tape.

Intraoperative

Surgical Steps

1. **Anesthesia and Patient Positioning.** The procedure was described initially as an ambulatory surgical procedure performed under local anesthesia. However, it also can be performed with regional or general anesthesia. The rationale for local anesthesia is that a cough stress test can be performed after placement of the tape to allow for proper tension setting of the tape. If performed without other surgeries, TVT in most cases is a day-surgery procedure. The operation is performed in the high lithotomy position. The vagina is surgically prepared, and an 18F Foley catheter is placed to assist in deflection of the urethra during needle passage.

2. **Abdominal Incisions.** Two Â½-cm skin incisions are created 1 cm above the symphysis and 1 cm lateral to the midline. Although many surgeons incise the skin more laterally, we believe that midline incisions decrease the risk of major vessel injury and do not increase the risk of bladder perforation.

3. **Vaginal Incisions.** A midline incision is made sharply in the vaginal epithelium beginning 1 cm proximal to the urethral meatus and is extended 2 cm cephalad. Allis clamps are placed on the edges of the vaginal incision for traction. Using Metzenbaum scissors, bilateral submucosal tunnels are created beneath the vaginal epithelium on either side of the urethra. These tunnels extend several centimeters toward the ipsilateral pubic rami to allow placement of the TVT needle.

4. **Catheter Guide Placement.** A rigid guide is placed through the Foley catheter. During passage of the TVT needles, a surgical assistant uses the catheter guide to deflect the urethra to the contralateral side to prevent urethral injury.

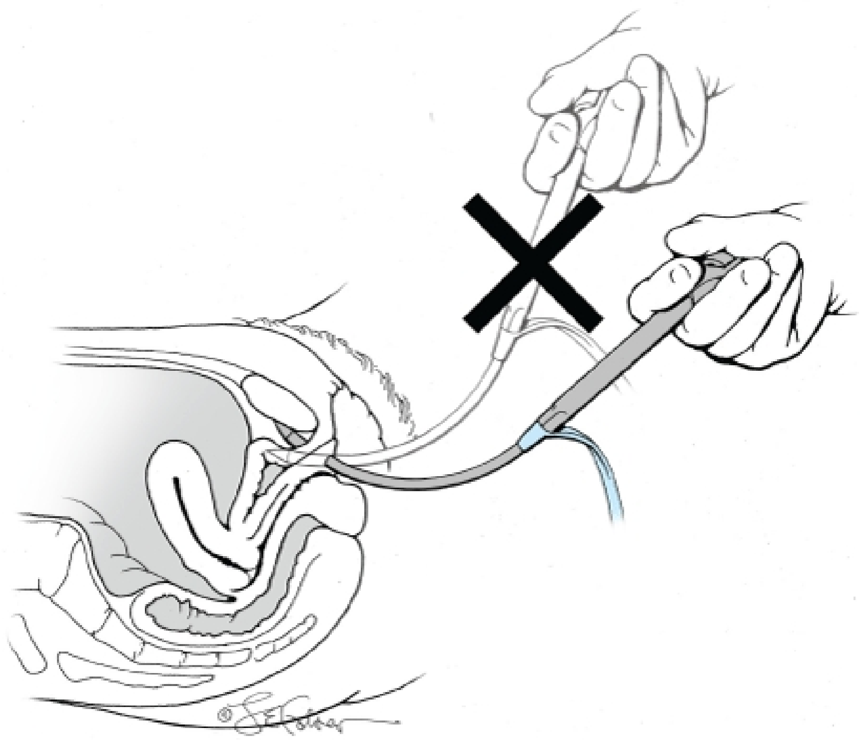
5. **Mesh Placement.** The TVT needle and mesh are attached to the introducer. The needle is placed through the submucosal tunnel so that its point touches the front surface of the pubic rami (Fig. 42-3.1). A hand placed in the vagina then carefully guides the needle around the back of the rami and up toward the abdominal incision (Fig. 42-3.2). The needle always should be directly behind the pubic bone. Pressure is applied to the introducer handle with the other hand, but the vaginal hand always controls the needle's direction. The handle of the introducer always should remain parallel to the ground to avoid lateral excursion into vessels (Fig. 42-3.3). Additionally, after the needle is passed around the pubic rami and behind the symphysis, its tip always should be directed toward the abdominal wall. The bladder may be perforated if excessive pressure is applied and if the needle is aimed cephalad rather than toward the abdominal wall. Small changes in position of the hand applying pressure to the handle may lead to bladder perforation.

FIGURE 42-3.1

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Needle placed through submucosal tunnel.

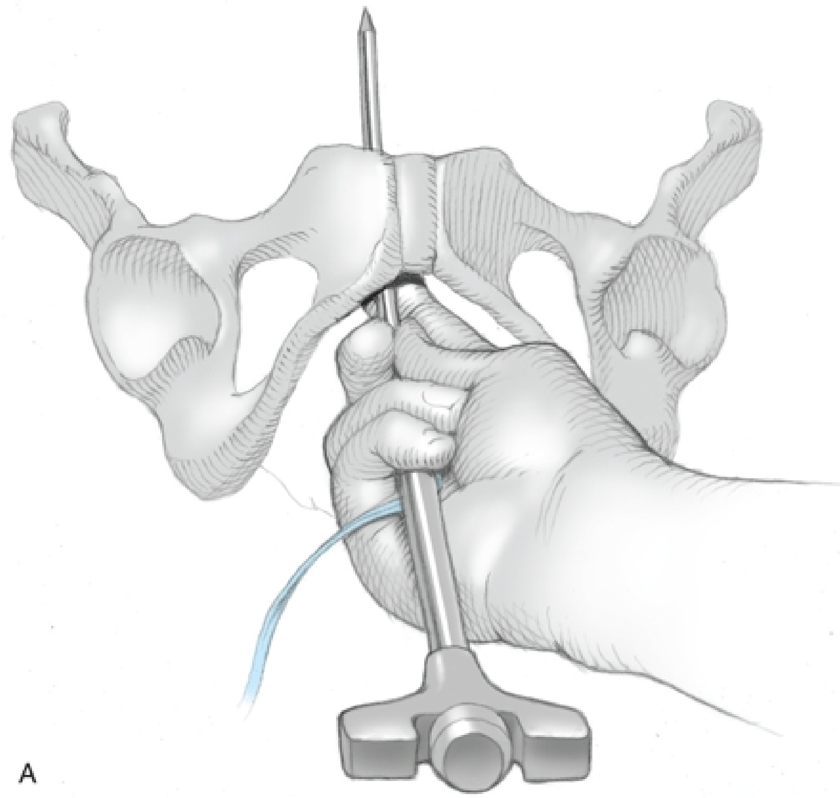
FIGURE 42-3.2



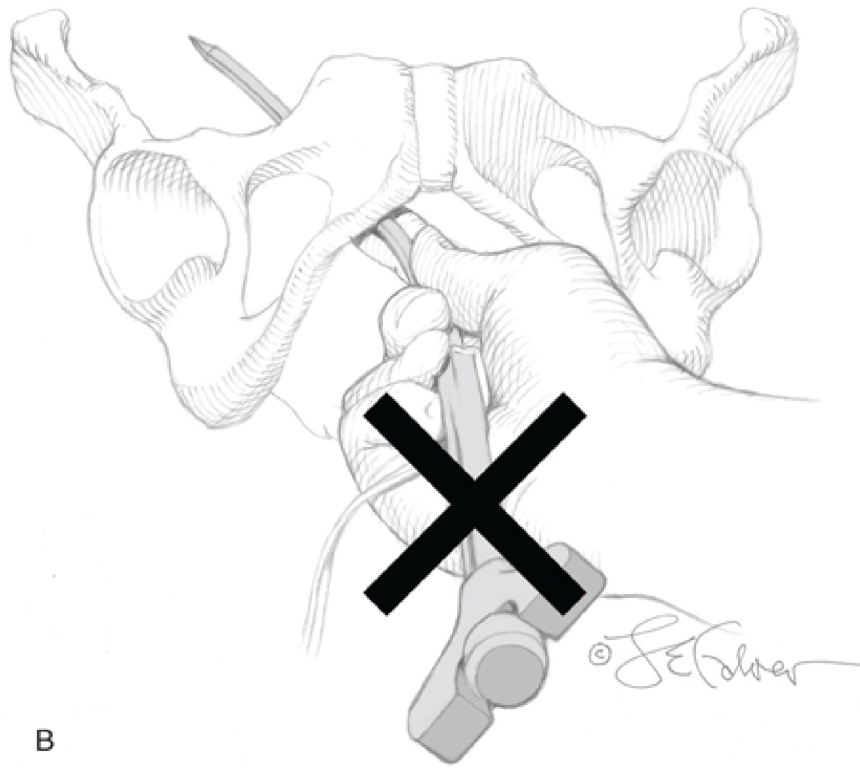
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Correct *(dark introducer)* and incorrect *(light introducer)* hand and introducer positioning.

FIGURE 42-3.3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com



B

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

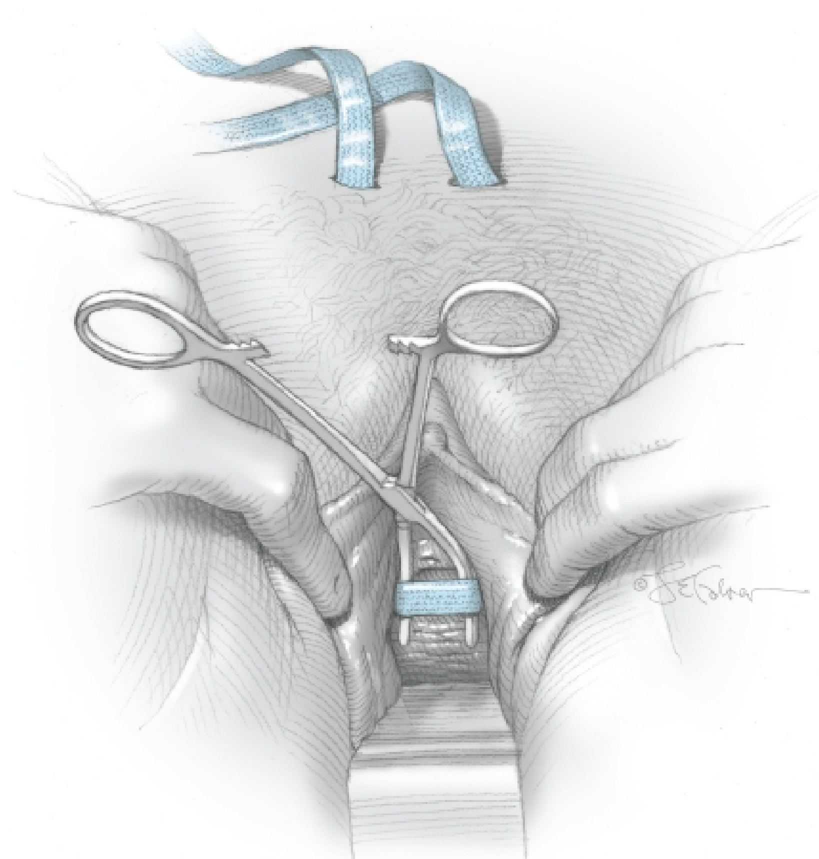
Correct and incorrect introducer positioning. **A.** Dark introducer, correct position. The tip is directed in the midline to a position behind the pubic bone. The handle is parallel to the ground. **B.** White introducer, incorrect position. The tip is directed laterally.

6. **Cystoscopy.** After the needle perforates the abdominal wall, the Foley catheter and catheter guide are removed. Cystoscopy is performed with a 70-degree cystoscope. During this, the bladder is distended with 200 to 300 mL of fluid, and inspection for perforation is completed. Generally, perforation will be obvious, and the TVT needle will be seen entering and exiting the bladder. In this situation, the needle is removed and replaced.

   After cystoscopy, the introducer is unscrewed from the needle, and the needle is brought through the abdominal wall. The needle is cut from the mesh, and the mesh is held with a hemostat. Next, a TVT needle is placed on the other side of the urethra, and cystoscopy is repeated.

7. **Setting Mesh Tension.** A hemostat is placed and opened between the urethra and mesh to act as a spacer and create distance between the mesh and urethra (Fig. 42-3.4). This spacing avoids excessive elevation of the urethra and lowers the risk for postoperative urinary retention.

FIGURE 42-3.4

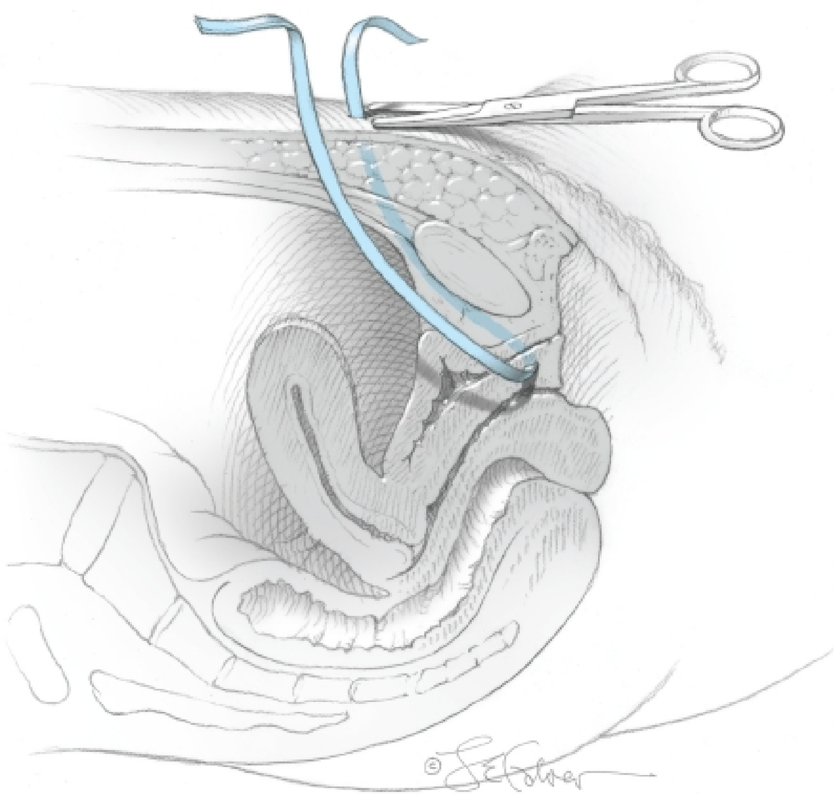


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Setting mesh tension.

8. **Sheath Removal.** An assistant surgeon then removes the plastic covering of the mesh while the surgeon holds the mesh at the desired distance from the urethra using the hemostat. The plastic covering should be removed with a minimal amount of tension to avoid mesh stretching. The mesh is trimmed at the abdominal incisions (Fig. 42-3.5).

FIGURE 42-3.5



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Sheath removal and tape trimming.

9. **Wound Closure.** The vaginal incision is closed in a running fashion with 2-0 delayed-absorbable suture. The abdominal incisions may be closed with skin adhesive or with a single interrupted 4-0 delayed-absorbable skin suture.

Postoperative

Prior to discharge from a day-surgery unit, an active voiding trial is performed (see Chap. 39, Voiding Trials). If the patient fails this trial, a Foley catheter remains. A second voiding trial can be repeated in a few days or at the surgeon's discretion. Alternatively, a woman can be taught self-catheterization. This is continued until postvoid residuals fall below 100 mL.

Normal diet and activity can resume during the first postoperative days. Intercourse, however, should be delayed until the vaginal incision is healed. The time to resumption of exercise and strenuous physical activity is controversial. A standard recommendation has been to delay these at least 2 months, although there are no data to support this. However, logic would suggest that this is a reasonable amount of time allow adequate healing.

42-4 TRANSOBTURATOR TAPE SLING

The transobturator tape (TOT) sling procedure is a variation of the midurethral sling procedures, which began with tension-free vaginal tape (TVT). The procedure is gaining popularity, although data regarding its long-term success are still not available. The procedure has several important differences from TVT, and there are also several modifications of the TOT procedure itself.

Generally, TOT is indicated for primary stress urinary incontinence (SUI) secondary to urethral hypermobility (see Chap 23, Midurethral Slings). It is currently not clear whether TOT will be of value in patients who have SUI secondary to intrinsic sphincteric deficiency.

During TOT procedures, a permanent sling material is placed bilaterally through the obturator fascia and extends underneath the midurethra. The entry point overlies the proximal tendon of the adductor longus muscle. Because of this entry approach, the space of Retzius is avoided. Bleeding in the space of Retzius is one of the primary complications of TVT, and avoidance of this space is an attractive TOT feature. Additionally, in patients who have had prior anti-incontinence procedures and have scarring in the space of Retzius, bladder perforation may be averted by avoiding dissection in this space.

Kits containing the required mesh and placement needles for TOT are produced by several companies, and each has its own modifications. The two major types of TOT procedures are defined by whether needle placement begins inside the vagina and is directed outward, termed an *in-to-out approach,* or starts outside and is directed inward, called an *out-to-in approach.* Currently, the out-to-in technique is performed more commonly and is described below.

Preoperative

PATIENT EVALUATION

Prior to surgery, patients undergo complete urogynecologic evaluation. Urodynamic testing is recommended to differentiate stress and urge incontinence. Many patients have mixed incontinence, and those whose stress symptoms predominate would be appropriate candidates.

Of note, caution must be exercised in patients who are Valsalva voiders. These women void with abdominal straining rather than with detrusor contraction and urethral relaxation. Most incontinence procedures prevent leakage by closing the urethra during cough or Valsalva maneuver. Therefore, these surgeries, when performed in women who rely on the Valsalva maneuver to urinate, often will results in voiding dysfunction.

CONSENT

As with other surgeries for incontinence, the major risks of this procedure are development of urge incontinence, voiding dysfunction, urinary retention, and failure to correct stress incontinence. Groin pain appears to be another potential postoperative problem. Long-term complications may be associated with the supporting mesh and include mesh erosion. Prior to surgery, patients should have realistic expectations and be informed of success rates in the literature as well as those of the individual surgeon. Moreover, the definition of *outcome success* varies from woman to woman. For example, in a patient with severe incontinence and 20 leakage episodes per day, improvement to 1 leakage episode every other day would be considered successful. However, in a woman with rare leakage, it may be more difficult to achieve an outcome considered satisfactory. For this reason, patient's expectations should be discussed prior to surgery.

Intraoperatively, there is some risk of bladder perforation, although it is believed to be significantly less than that with TVT. There also may be risk of urethral perforation. Lastly, inappropriate TOT trocar placement can lead to significant hemorrhage if major pelvic vessels are lacerated.

PATIENT PREPARATION

Bowel preparation is based on surgeon preference and on concurrent surgeries planned. Antibiotic prophylaxis is given.

Intraoperative

INSTRUMENTS

A TOT kit will contain two TOT needles and synthetic mesh tape (see Fig. 23-11). The TOT needle is designed to navigate the path from the entry point around the pubic rami. The needle then exits the vagina at a midpoint along the urethra's length.

A plastic sheath surrounds the mesh tape and allows the mesh to be pulled into position smoothly. However, once these plastic sheaths are removed, the mesh remains fixed in position.

Surgical Steps

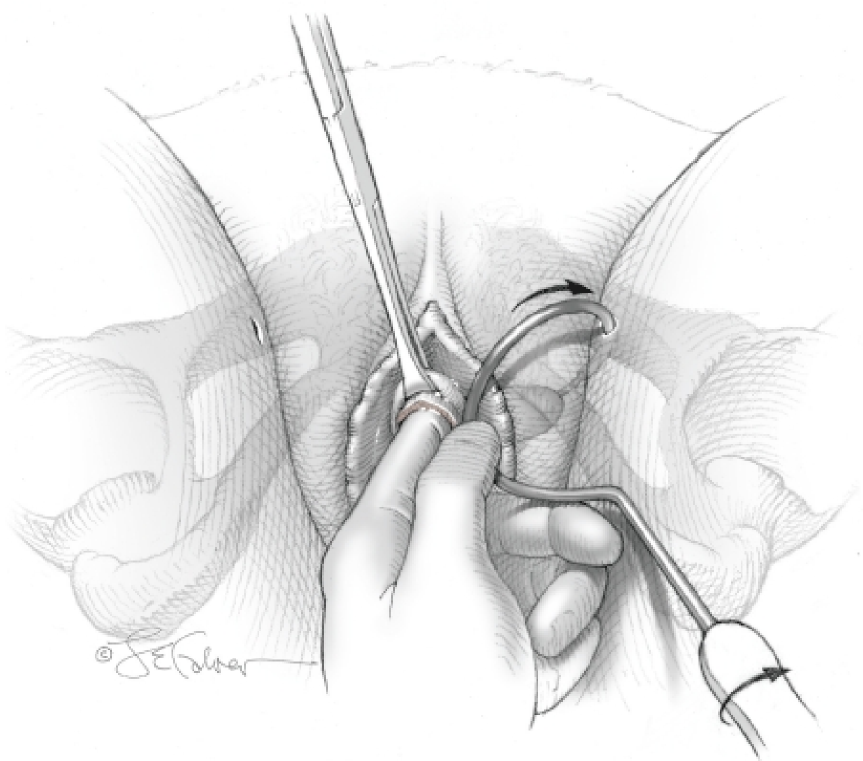
1. **Anesthesia and Patient Positioning.** If performed without other surgeries, a TOT procedure in most cases is a day-surgery procedure. It is performed in high lithotomy position under general, regional, or local anesthesia. The vagina is surgically prepared, and a Foley catheter is placed to assist in determination of urethral location.

2. **Vaginal Incisions.** A midline incision is made sharply in the vaginal epithelium beginning 1 cm proximal to the urethral meatus and is extended 2 to 3 cm cephalad. Allis clamps are placed on the edges of the vaginal incision for traction. Using Metzenbaum scissors and blunt finger dissection, bilateral submucosal tunnels are created beneath the vaginal epithelium on either side of the urethra. These tunnels extend up to and behind the iliopubic rami.

3. **Thigh Incisions.** A 0.5- to 1-cm entry incision is made bilaterally in the thigh crease skin at a point 4 to 6 cm lateral to the clitoris, and at the site where the adductor longus insertion can be palpated.

4. **Mesh Placement.** The TOT needle is grasped, and the tip is placed in one of the thigh incisions (Fig. 42-4.1). The tip is directed cephalad until the obturator membrane is perforated, and a "popping" sensation is felt. A vaginal finger is placed in the ipsilateral vaginal tunnel and is positioned up to and behind the iliopubic rami. Using the curve of the TOT needle, the surgeon then directs the needle tip to the end of his finger and passes the needle into the vagina (Fig. 42-4.2). The TOT mesh is attached to the end of the needle, and the needle is withdrawn through the thigh incision (Fig. 42-4.3). The procedure is repeated on the other side.

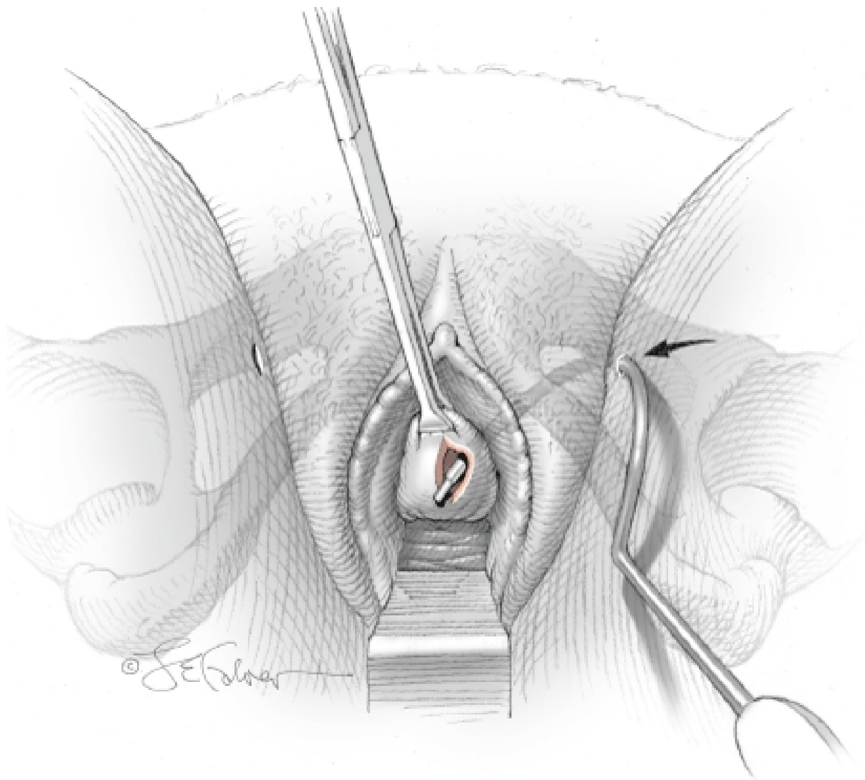
FIGURE 42-4.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Needle introduction.

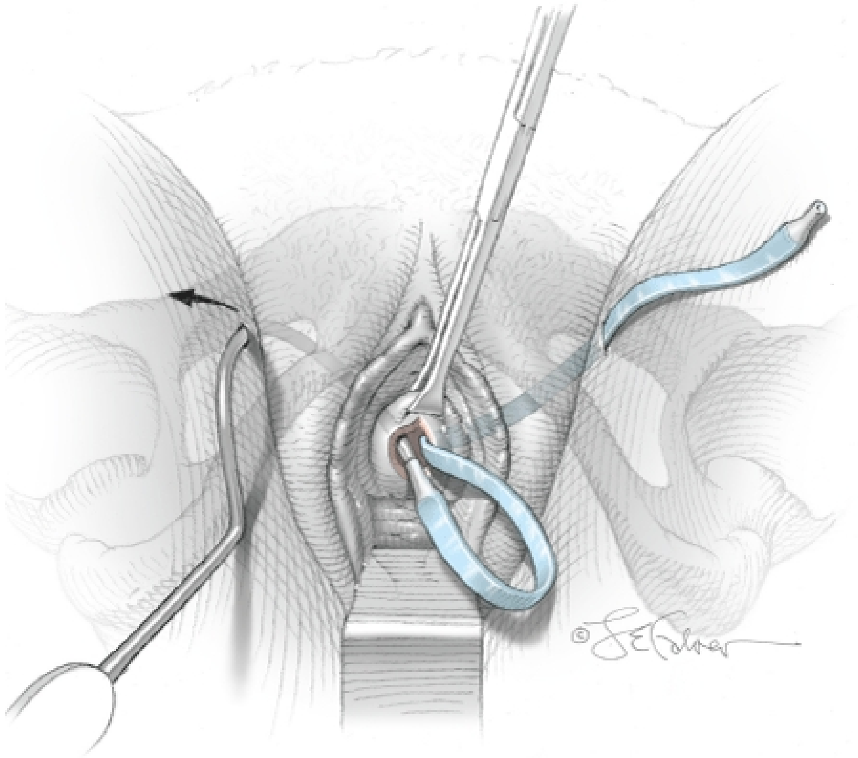
FIGURE 42-4.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Needle passage.

FIGURE 42-4.3

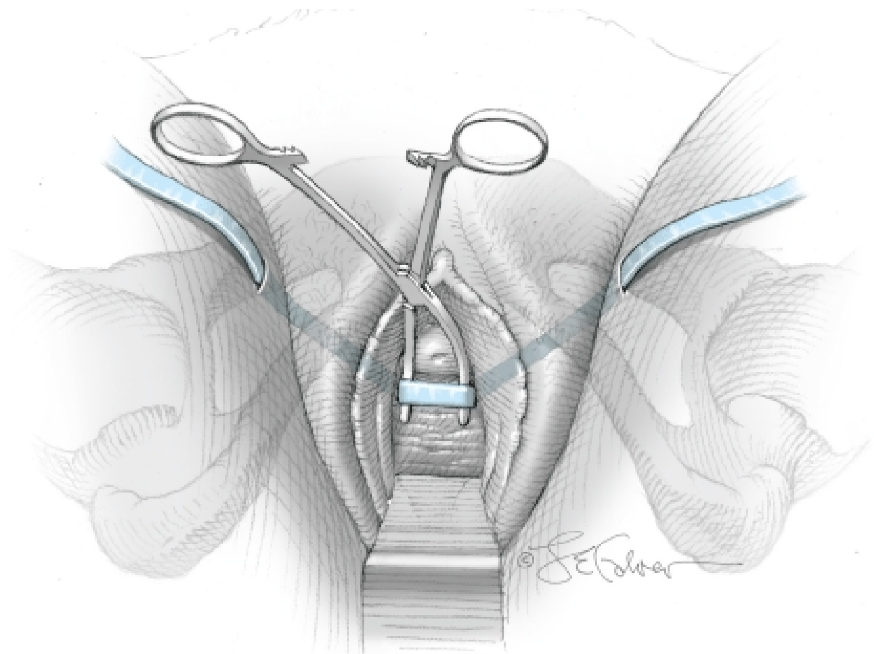


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Tape placement.

5. **Setting Mesh Tension.** A hemostat is placed and opened between the urethra and mesh to act as a spacer and create distance between the mesh and the urethra (Fig. 42-4.4). This spacing avoids excessive elevation of the urethra and lowers the risk for postoperative urinary retention.

FIGURE 42-4.4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Setting mesh tension.

6. **Sheath Removal.** An assistant surgeon then removes the plastic covering of the mesh through the thigh incision while the surgeon holds the mesh at the desired distance from the urethra using the hemostat. The plastic covering should be removed with a minimal amount of tension to avoid mesh stretching. The mesh is trimmed at the thigh incisions.

7. **Wound Closure.** The vaginal incision is closed in a running fashion with 2-0 delayed-absorbable suture. The thigh incisions may be closed with a single interrupted subcuticular suture with 4-0 delayed-absorbable suture or other suitable skin closure methods.

8. **Cystoscopy.** The procedure is marketed as one in which cystoscopy is not necessary. However, because bladder and urethral injury can occur, we recommend postprocedural cystoscopy.

Postoperative

Prior to discharge from the day-surgery unit, an active voiding trial is performed (see Chap. 39, Voiding Trials). If the patient fails this trial, a Foley catheter remains. A second voiding trial can be repeated in a few days or at the surgeon's discretion. Alternatively, a patient can be taught self-catheterization. This is continued until postvoid residuals fall below 100 mL.

Normal diet and activity can resume during the first postoperative days. Intercourse, however, should be delayed until the vaginal incision is healed. The time to resumption of exercise and strenuous physical activity is controversial. A standard recommendation has been to delay these at least 2 months, although there are no data to support this. However, logic would suggest that this is a reasonable amount of time allow adequate healing.

42-5 PUBOVAGINAL SLING

Pubovaginal sling is a standard procedure for stress urinary incontinence (SUI). Traditionally, it has been used for SUI stemming from intrinsic sphincteric deficiency, which is characterized by a nonmobile urethra, a low maximum urethral closing pressure, or

low Valsalva leak point pressure (see Chap. 23, Pubovaginal Slings). In addition, this procedure also may be indicated for patients with prior failed anti-incontinence operations. It is generally not employed in a woman having her first anti-incontinence operation.

In the past, different materials have been used for the sling. However, autologous fascia currently is preferred. Generally, autologous fascia is obtained from the rectus sheath, although fascia lata from the thigh alternatively may be used. With this surgery, a strip of fascia is placed at the bladder neck through the space of Retzius, and ends are secured above the rectus abdominis muscle.

Preoperative

PATIENT EVALUATION

As with other anti-incontinence procedures, patients require urogynecologic evaluation including urodynamic testing to confirm SUI and intrinsic sphincteric deficiency. Additionally, SUI often accompanies pelvic organ prolapse. Thus, the need for concurrent repair of associated prolapse should be assessed prior to surgery.

CONSENT

In addition to general surgical risks, patients should be counseled regarding the risk of recurrent incontinence and urinary retention following surgery.

PATIENT PREPARATION

Antibiotic prophylaxis with a first- or second-generation cephalosporin at the time surgery is recommended. Bowel preparation is performed the evening before surgery.

Intraoperative

Surgical Steps

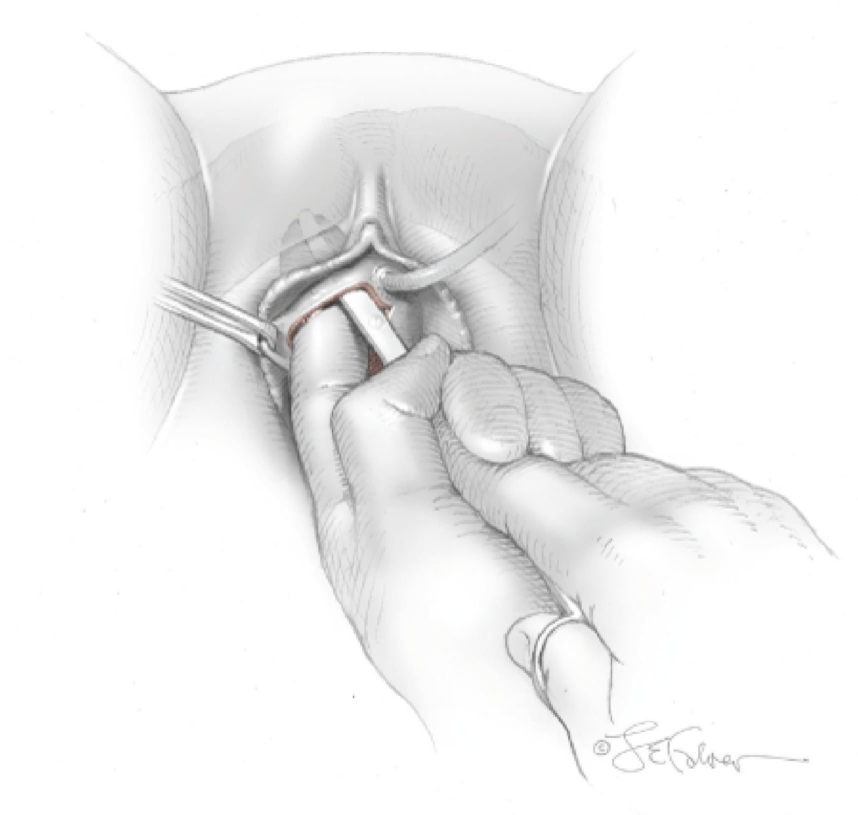
1. **Anesthesia and Patient Positioning.** Pubovaginal sling may be performed under general or regional anesthesia as an inpatient procedure. The patient is placed in a high lithotomy position, and the legs are held by candy-cane stirrups. The abdomen and vagina are surgically prepared, and a Foley catheter is placed.

2. **Graft Harvest.** A transverse skin incision is made 2 to 4 cm above the symphysis and should be large enough to allow removal of a fascial strip that measures, at minimum, 2 × 6 cm. The incision is carried down through subcutaneous tissue to the fascia.

   The fascia to be harvested is outlined and then dissected sharply and removed. Following removal, the strip is cleaned of fat and adventitial tissue. A helical stitch using 0-gauge polypropylene suture then is placed against the grain of the fascia at each end of the strip. These sutures are not tied. The fascial incision then is closed in a running fashion with 0-gauge delayed-absorbable suture.

3. **Vaginal Incision.** Two centimeters proximal to the urethral meatus, a 5- to 6-cm midline vertical incision is made sharply in the anterior vaginal wall. Sharp and blunt dissection is used to lift the vaginal epithelium off the underlying fibromuscular layer. The space of Retzius is entered bluntly or sharply bilaterally by penetrating the perineal membrane (Fig. 42-5.1). This membrane was previous termed the *deep fascia of the urogenital diaphragm* (see Fig. 38-28). The surgeon's finger should palpate the pubic bone in the space of Retzius (Fig. 42-5.2). Bleeding may be encountered, and this can be managed with compression or suturing.

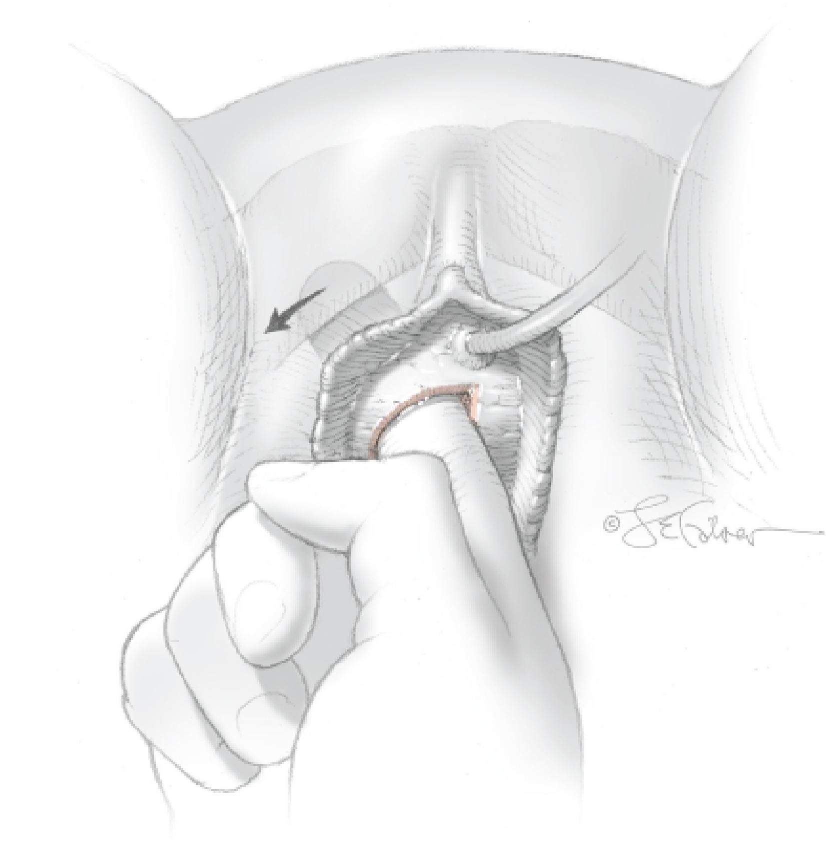
FIGURE 42-5.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Entry into the space of Retzius.

FIGURE 42-5.2



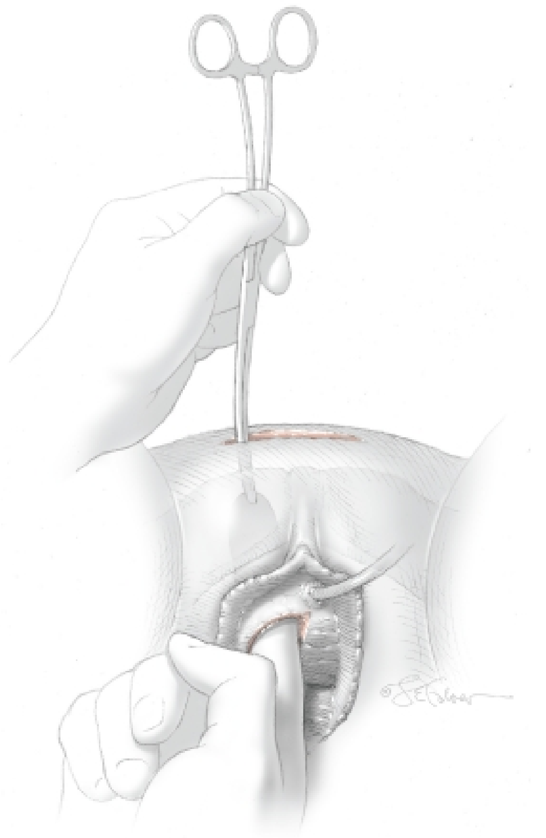
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Palpation of pubic bone.

4. **Fascia Placement.** A long dressing or packing forceps or needle ligature carrier is used from above to perforate the rectus sheath below the prior harvest incision. The instrument is placed against the back of the pubic bone and advanced toward the vagina. Concurrently, the surgeon guides the instrument to his or her finger within the space of Retzius (Fig. 42-5.3).

   The suture at one end of the fascial strip is grasped with the forceps and threaded up through the abdominal incision on one side of the urethra. A similar procedure is performed on the opposite side of the urethra with the other end of the sling. As a result, the fascial sling lies positioned below the bladder neck (Fig. 42-5.4). Three to four 2-0 delayed-absorbable sutures are used to fix the sling beneath the bladder neck to prevent movement.

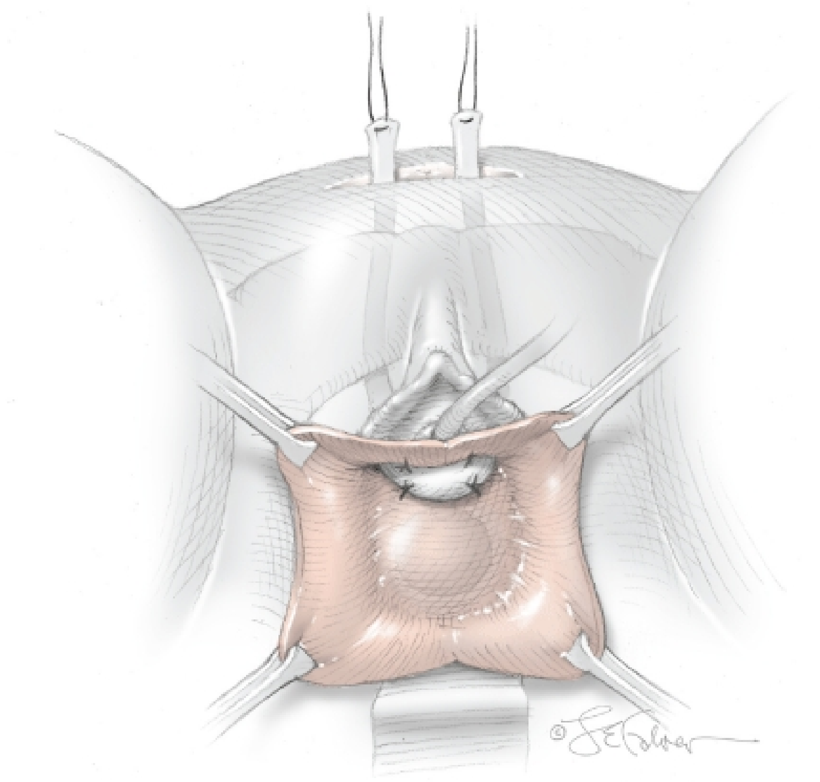
FIGURE 42-5.3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Fascial strip placement.

FIGURE 42-5.4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Fascial sling sutured in place.

5. **Setting Sling Tension.** Sutures attached to the sling ends then are tied together above the rectus sheath. During knot tying, a space of two to three fingerbreadths is left between the knot and fascia to prevent bladder neck obstruction and urinary retention. After the knot is secured, there should be no upward angulation of the urethra or bladder neck.

6. **Cystoscopy.** Cystoscopy is performed to exclude bladder perforation and ureteral obstruction.

7. **Vaginal Incision.** The vaginal incision is closed with 2-0 delayed-absorbable suture in a running fashion. A Foley catheter is left in place. In the past it was common practice to insert a suprapubic tube. However, with a trend toward setting tension loosely on the sling, the risk of prolonged urinary retention is lowered, and suprapubic drainage therefore is not typically required.

8. **Abdominal Incision.** The abdominal incision is closed as described in Section 41-2, Pfannenstiel Incision.

Postoperative

In general, recovery follows that associated with laparotomy and depends heavily on incision size. A voiding trial as described in Chapter 39, Voiding Trials is performed prior to hospital discharge.

42-6 URETHRAL BULKING INJECTIONS

Injection of bulking agents into the urethral submucosa is one method available to treat stress urinary incontinence (SUI) resulting from intrinsic sphincter deficiency (ISD) (see Chap. 23, Periurethral Bulking Agents). Although mechanisms are not completely

clear, effectiveness may result from expansion of the urethral walls, which allows them to better approximate or *coapt* (Kershen, 2002). As a result, intraluminal resistance to flow is increased, and continence is restored (Winters, 1995). As another effect, injections elongate the functional urethra, and this may allow more even distribution of abdominal pressures across the proximal urethra to resist opening during stress (Monga, 1997).

Although traditionally recommended for treatment of SUI solely due to ISD, some evidence suggests that it can be used to treat SUI resulting from combined ISD and urethral hypermobility (Bent, 2001; Herschorn, 1997; Steele, 2000).

Urethral injection offers a cystoscopically assisted, minimally invasive treatment of SUI that can be performed in an office setting under local anesthesia and is associated with a low risk of complications. For these reasons, it is often chosen for women who wish to avoid surgery or who are not surgical candidates because of other health reasons. Urethral injections can be performed both peri- and transurethrally. The transurethral approach is used more commonly and allows for more accurate placement of the bulking agent (Faerber, 1998; Schulz, 2004).

Currently available agents in the United States approved for use include bovine collagen, autologous fat, and several synthetic agents. Of these, collagen is used most commonly in the United States.

Preoperative

PATIENT EVALUATION

Complex urodynamic testing with assessment of urethral structure and function should be completed. Maximum urethral closure pressure or leak point pressure is specifically evaluated (see Chap. 23, Multichannel Cystometrics). Additionally, urethral mobility should be assessed with Q-Tip testing or similar evaluation (see Fig. 23-8)

CONSENT

Patients should be informed that although success rates in general are lower than those for surgery, 1-year rates of curing or improving SUI range from 60 to 80 percent (Bent, 2001; Corcos, 2005; Lightner, 2002; Monga, 1995). Continence rates diminish with time, as would be intuitive with the breakdown of collagen and fat. However, Chrouser (2004) found similar rates of decline with time even when synthetic material was compared with collagen. Accordingly, these injections should be viewed as a nonpermanent treatment of SUI, with sustained continence found in only 25 percent of patients at 5 years following injection (Gorton, 1999).

One major advantage to urethral injection is its low associated risk of complications. Side effects of collagen injection generally are transient and may include vaginitis, acute cystitis, and voiding dysfunction symptoms. Of these, urinary retention for a few days after the procedure is the most common. Long-term retention, however, is not a significant risk. A more serious complication is persistent de novo urgency, which may develop in as many as 10 percent of women following injection (Corcos, 1999, 2005). In addition, allergic reaction is a possibility. Therefore, skin testing with a 0.1-mL intradermal test injection is recommended 1 month prior to the first injection (CR Bard, Inc., 2000).

ANTIBIOTIC PROPHLYAXIS

Urinary tract infection commonly can follow urethral injection. Therefore, a suitable antibiotic is administered orally after the procedure is complete.

Intraoperative

CHOICE OF BULKING AGENT

In the United States, several agents are currently available for urethral injection: autologous fat, bovine collagen, carbon-coated synthetic microspheres (Durasphere, Carbon Medical Technologies, Inc., St. Paul, MN), calcium hydroxyapatite particles (Coaptite, Boston Scientific, Natick, MA), and ethylene vinyl alcohol copolymer (Tegress, C.R. Bard, Inc., Covington, GA). The more commonly used agent in the United States is Contigen (C.R. Bard, Inc., Covington, GA), a suspension containing purified bovine collagen that has been crosslinked with glutaraldehyde.

However, because collagen lacks durability over time, other agents have been investigated as bulking agents. Autologous fat

provides limited success in the treatment of SUI owing to rapid degradation and re-absorption. For this reason, it is not employed primarily for this use (Haab, 1997; Lee, 2001). Synthetic agents also are available and effective, but long-term comparative studies with collagen are currently lacking (Chrouser, 2004; Lightner, 2002).

Surgical Steps

1. **Anesthesia and Patient Positioning.** Urethral injection for most patients can be performed in an office setting with cystoscopy capability. The patient is placed in dorsal lithotomy position, the vulva is surgically prepared, and the bladder is drained. Two-percent lidocaine jelly is instilled into the urethra 10 minutes prior to the procedure. If necessary, topical 20-percent benzocaine can be used as an analgesic on the vulva, and 4 mL of 1-percent lidocaine can be injected in divided doses at the 3 and 9 o'clock positions of the urethra.

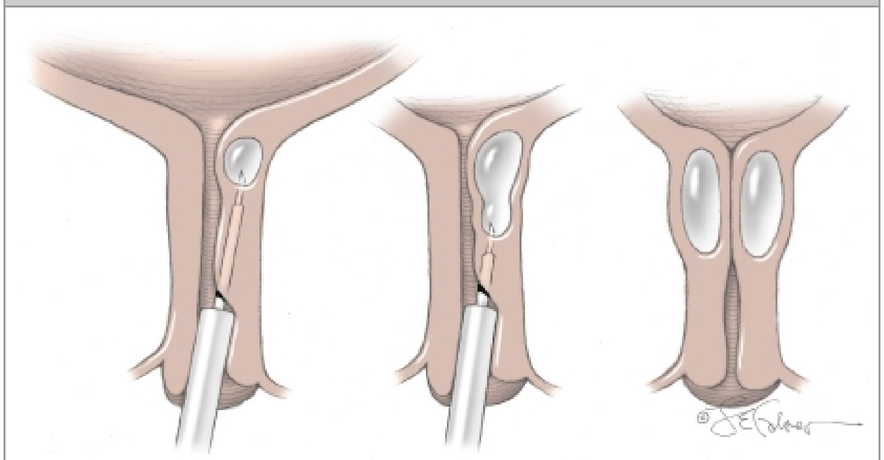
2. **Transurethral Approach: Needle Placement.** A cystoscope is positioned within the distal urethra so that the midurethra, proximal urethra, and bladder neck are viewed simultaneously. A 22-gauge spinal needle attached to a syringe carrying the bulking agent is introduced through the cystoscopic sheath. With the bevel pointing toward the urethral lumen, the needle is directed at a 45-degree angle to the lumen and is inserted into the urethral wall at the 9 o'clock position and at the level of the midurethra.

   After the needle tip penetrates the urethral wall and the bevel is no longer seen, the needle is advanced parallel to the urethral lumen for 1 to 2 cm. This positions the needle at the level of the proximal urethra.

3. **Injection.** The bulking agent is injected under constant pressure, and the submucosal lining begins to rise (Fig. 42-6.1). The needle is withdrawn slowly to bulk the proximal and midurethra. Bulking agent is administered until coaptation of the mucosa has developed (Fig. 42-6.2). In general, one to two syringes (2.5 to 5 mL) of collagen are used per procedure. These steps then are repeated at the 3 o'clock position.

   Ideally, the number of needle holes made into the urethral wall should be minimized to avoid leakage of bulking agents through these punctures. Thus, if a second syringe of agent is required to achieve coaptation, the originally positioned needle remains in place, and a second syringe of agent is attached.

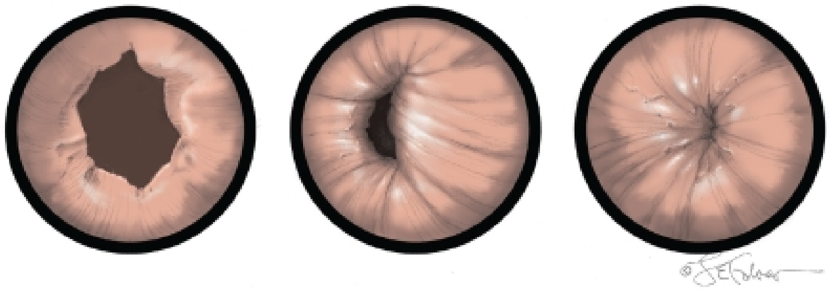
FIGURE 42-6.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Injection of bulking agent.

FIGURE 42-6.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Corresponding cystoscopic views of urethral coaptation as bulking agent is injected, as shown in Figure 42-6.1.

4. **Cystoscope Removal.** Once coaptation of the mucosa is achieved, as the cystoscope is removed, care should be taken not to advance it proximal to the injection site. This avoids forceful compression of the deposited agent.

Postoperative

Women are discharged home following their first postinjection voiding. Oral antibiotic prophylaxis is recommended. Women should abstain from intercourse for 10 days following injection but otherwise may resume usual activities.

If urinary retention develops, then intermittent self-catheterization (ISC) is begun and continued until retention resolves. If a woman is unable to perform ISC, a temporary Foley catheter is placed. However, catheter placement potentially can compress deposited bulking agent collagen and diminish urethral coaptation.

Two weeks following injection, it is our practice to assess treatment success. If patients fail to achieve desired degrees of continence, additional injections are planned to improve urethral coaptation.

42-7 URETHROLYSIS

Uretholysis is the loosening or release of a previous urethral suspension repair. This type of release is used in women with symptoms of urethral obstruction, including urinary retention and voiding dysfunction, following suspension. It can be performed either vaginally or abdominally. A vaginal approach is used predominantly and can mobilize the urethra and bladder neck successfully. An abdominal approach, however, may afford a better opportunity to mobilize the bladder from the pubic symphysis and also may be selected in instances in which the initial surgery was performed via laparotomy.

Debate exists as to the need of a concurrent anti-incontinence procedure to compensate for urethral support lost with urethrolysis. In many cases, residual scarring prevents stress incontinence, and our belief is to avoid repeating a second potentially obstructing procedure.

Preoperative

PATIENT EVALUATION

In women with bladder neck obstruction, there is a temporal relationship between surgery and symptoms. Objective assessment with urodynamic testing is performed to determine the cause of voiding dysfunction and differentiate between a hypotonic bladder and obstruction. Obstruction may result from bladder neck obstruction or pelvic organ prolapse. Thus, a thorough examination for

prolapse should be included.

CONSENT

In addition to the usual surgical risks, bleeding may be a significant complication due to vascularity in the space of Retzius. Additionally, dissection of dense scarring around the urethra and bladder may place these structures at risk of laceration.

Patients should be counseled on potential surgical outcomes. First, because of re-formation of scar tissue, urethrolysis may fail to relieve symptoms. In contrast, postoperative incontinence may follow deconstruction of the prior anti-incontinence support.

PATIENT PREPARATION

Bowel preparation prior to urethrolysis is individualized. Antibiotic prophylaxis is administered prior to surgery to decrease risks of postoperative wound and urinary tract infection.

Intraoperative

VAGINAL APPROACH

Surgical Steps

1. **Anesthesia and Patient Positioning.** Urethrolyis may be performed under general or regional anesthesia. The patient is placed in the high lithotomy position using candy-cane stirrups. The vagina is surgically prepared, and a Foley catheter containing a 30-mL balloon is placed into the bladder.

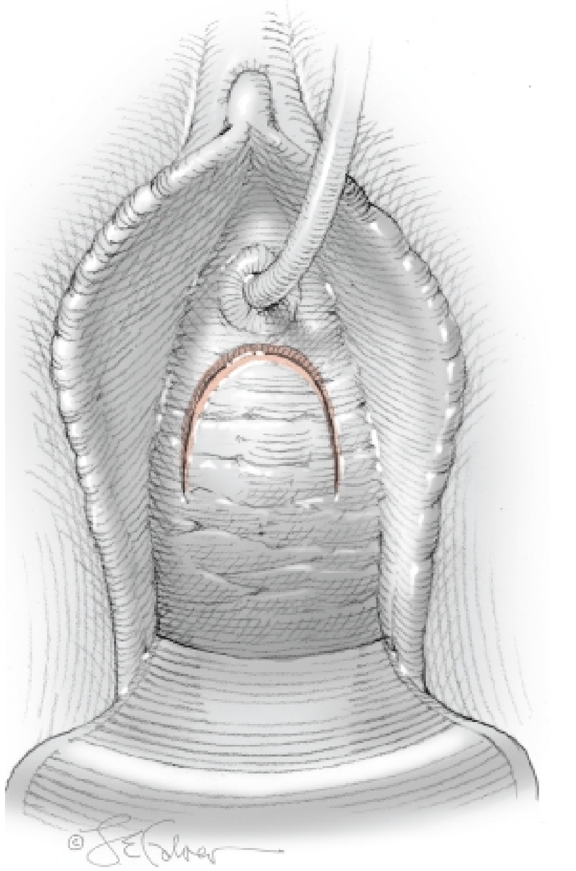
2. **Vaginal Incision.** Traction is placed on the Foley catheter to identify the bladder neck and assess the degree of scarring. Either a vertical midline or U-shaped incision is made in the anterior vaginal wall at the level of the proximal urethra and bladder

   (Fig. 42-7.1). Sharp dissection is used to separate the vaginal epithelium from underlying tissues and is extended bilaterally toward the inferior edge of each pubic rami.

   Dissection frees the urethra by dividing scar tissue or prior sling material between the urethra and pubic rami. If prior sling material is identified, this may be incised or excised, if necessary. Bleeding is encountered frequently and can be controlled with direct pressure or vessel ligation.

   After this lateral dissection, the urogenital diaphragm is perforated, and the space of Retzius is entered (Fig. 42-7.2). Careful blunt dissection within this space and at the back of the symphysis pubic additionally will assist in mobilizing the proximal urethra.

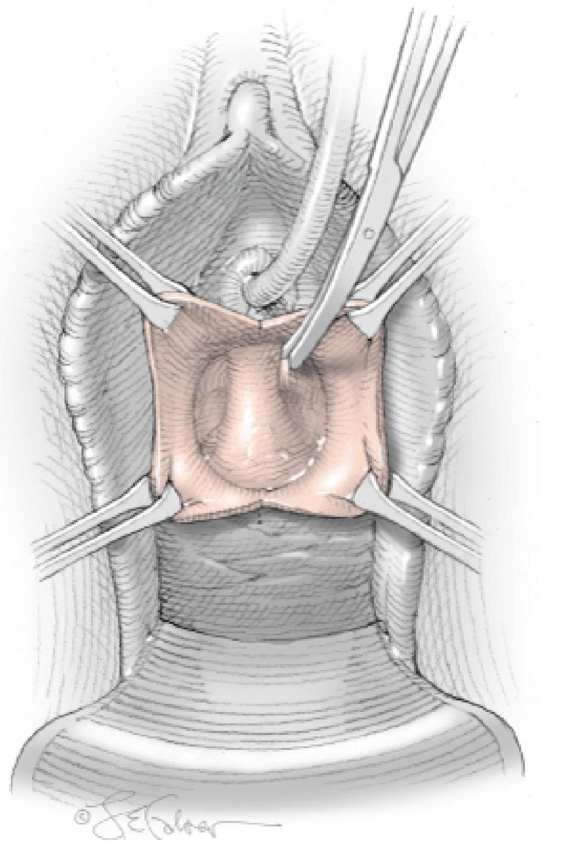
FIGURE 42-7.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Vaginal incision.

FIGURE 42-7.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Urethral dissection.

3. **Incision Closure.** Following adequate mobilization of the urethra, the vaginal incision is reapproximated with a running closure using 2-0 delayed-absorbable suture.

ABDOMINAL APPROACH

Surgical Steps

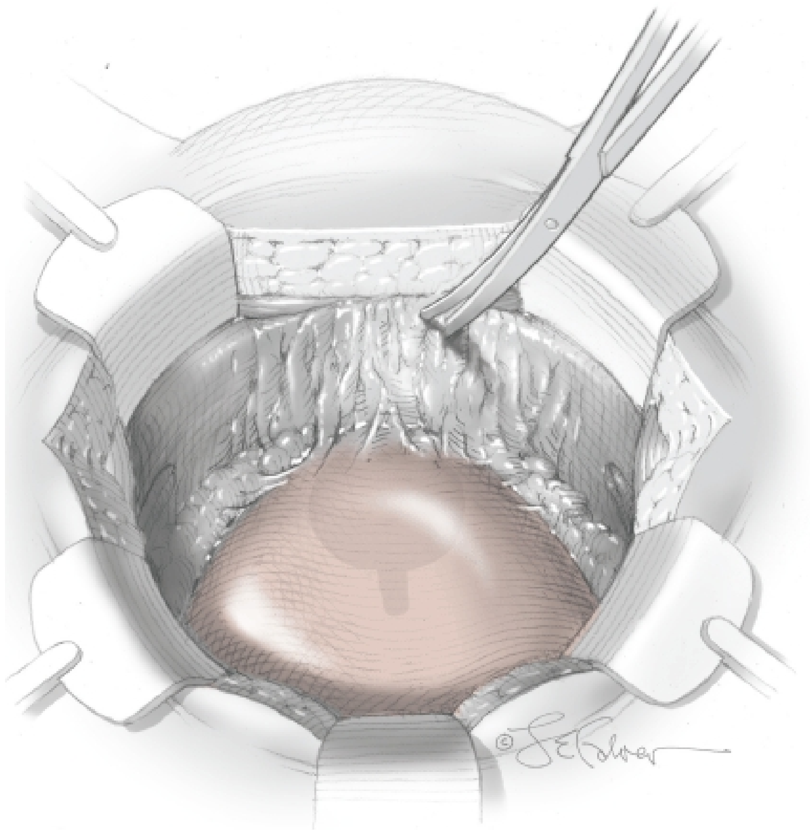
1. **Anesthesia and Patient Positioning.** As with a vaginal approach, urethrolyis may be completed under general or regional anesthesia. For an abdominal approach, Allen stirrups and standard lithotomy positioning are preferred. This allows vaginal access to the surgeon's hand during dissection. The abdomen and vagina are surgically prepared, and a Foley catheter containing a 30-mL balloon is placed within the bladder.

2. **Abdominal Incision.** A low transverse incision typically is preferred for this procedure to permit easy access to the space of Retzius. Either a Pfannenstiel or a Cherney incision usually is selected (see Sections 41-2, Pfannenstiel Incision and 41-3, Cherney Incision).

3. **Entry into the Space of Retzius.** The correct plane of dissection to enter the space of Retzius lies directly behind the pubic bone. Loose areolar tissue is gently dissected downward in a mediolateral fashion with fingers or sponge beginning immediately behind the pubic bone. If the correct plane is entered, this potential space opens easily. However, women requiring urethrolysis typically have had prior surgery within this space. As a result, tissue may be densely adhered, and

sharp downward dissection along the posterior surface of the symphysis may be needed to enter this space (Fig. 42-7.3).

FIGURE 42-7.3



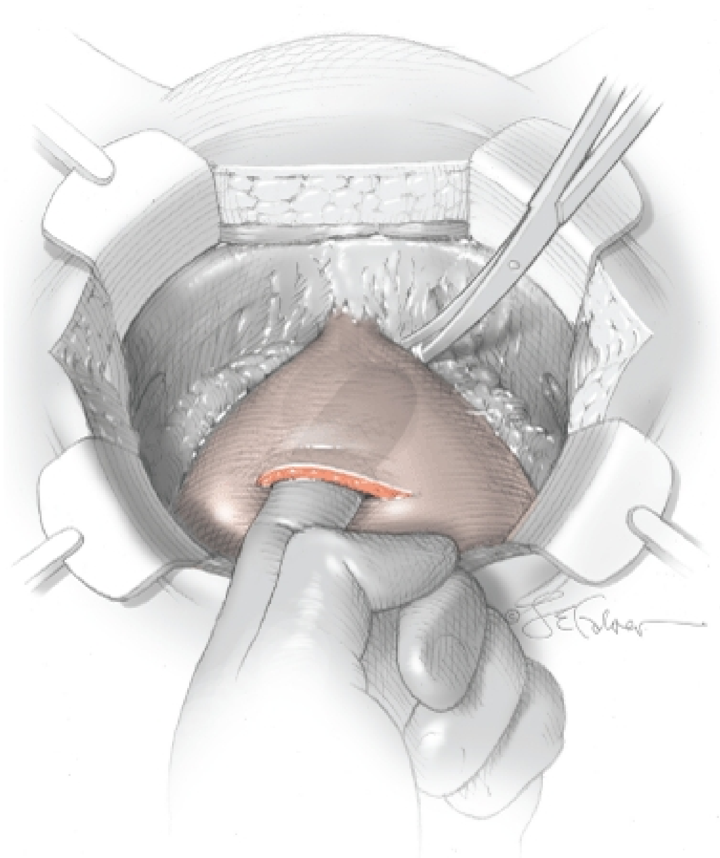
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Dissection in the space of Retzius.

4. **Bladder Dissection and Urethrolysis.** The bladder also typically is densely adhered to the back of the symphysis. Sharp dissection with the curved surface of scissors facing the symphysis is directed against the symphysis. This technique minimizes the risk of bladder laceration. At times, however, an intentional cystotomy may be required so that a finger can be placed inside the bladder to aid dissection (Fig. 42-7.4).

   Sharp dissection is continued inferiorly and laterally down the inner surface of the symphysis to free the bladder and eventually also the proximal urethra. Bleeding is common during dissection and may be controlled with sutures or clips.

FIGURE 42-7.4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Intentional cystotomy to aid bladder and urethral dissection.

5. **Abdominal Closure.** The abdomen is closed in a standard fashion (see Section 41-2, Pfannenstiel Incision).

Postoperative

An active bladder test is performed following catheter removal. If large residual volumes are found, intermittent self-catheterization or replacement of the catheter is required. If cystotomy was performed, the duration of catheterization depends on cystotomy size but typically is continued for several weeks.

42-8 MIDURETHRAL SLING RELEASE

Symptoms of obstruction may develop following urethral sling procedures, specifically tension-free vaginal tape (TVT) and transobturator tape sling (TOT) procedures. This complication develops in 4 to 6 percent of patients after TVT and generally is identified days to weeks after surgery. When obstruction is diagnosed, surgical release is indicated and involves simple cutting of the sling material.

Preoperative

PATIENT EVALUATION

Inability to fully empty the bladder may be due to urethral obstruction or a hypotonic bladder. New-onset urinary retention after a midurethral sling procedure (TVT or TOT) usually is due to sling tightness. However, there may be other factors involved, such as pre-existing or de novo bladder hypotonia. Therefore, prior to TVT urethrolysis, it is prudent to perform urodynamic testing to prove that symptoms are due to obstruction rather than to bladder hypotonia. Additionally, tape may erode into the bladder or urethra in cases of obstruction, and cystoscopy allows exclusion of this complication.

CONSENT

Associated with midurethral sling release, the risks of incontinence recurrence and intraoperative bladder or urethral injury should be considered in the consenting process.

PATIENT PREPARATION

This is a minor surgical procedure, and no specific patient preparation is required.

Intraoperative

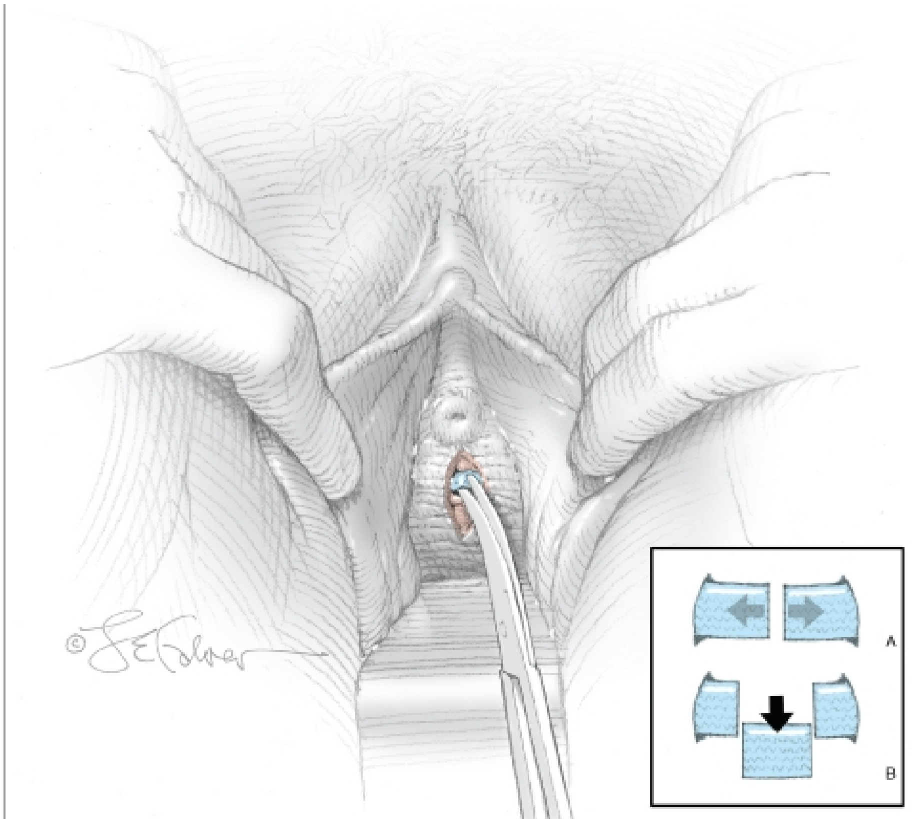
Surgical Steps

1. **Anesthesia and Patient Positioning.** This surgery can be performed with local, regional, or general anesthesia as an outpatient procedure. A patient is placed in high lithotomy position using candy-cane or Allen stirrups. The vagina is surgically prepared, and a Foley catheter is placed.

2. **Vaginal Incision and Tape Identification.** A midline suburethral incision that follows the prior primary surgical incision is made sharply. Careful dissection is used to expose the sling material and to define the urethral borders.

   Often because of increased sling tension, sling material is stretched and measures only half of its expected width. Additionally, there is usually extensive tissue ingrowth into the sling material, and identification and mobilization can be difficult (Fig. 42-8.1). Occasionally, a sling may migrate to the proximal urethra, and in these instances, the vaginal incision may require cephalad extension.

FIGURE 42-8.1



Mesh transection through vaginal incision. **A.** Mesh and retraction. **B.** Mesh excision.

3. **Incision of Sling Material.** After mobilization of the material, a hemostat is opened between the sling and urethra. Metzenbaum scissors are used to cut the sling material. In general, incision leads to immediate retraction of sling ends (Fig. 42-8.1A). If retraction does not follow, a 1-cm segment of material should then be excised (Fig 42-8.1B).

4. **Incision Closure.** After vigorous irrigation, the vaginal epithelium is closed in a continuous running fashion using 2-0 delayed-absorbable suture.

Postoperative

Prior to discharge, an active voiding trial is performed. If a Foley catheter remains, a second voiding trial can be repeated in a few days or at the surgeon's discretion. If a woman is performing self-catheterization, this is continued until postvoid residuals fall below 100 mL.

42-9 URETHRAL DIVERTICULUM REPAIR

The approach to urethral diverticulum repair varies and depends on the location, size, and configuration of the diverticular sac (see Chap. 26, Classification). For those that are near the bladder neck, partial ablation often is selected to avoid damage to the bladder neck and continence mechanism. For midurethral diverticulum, simple diverticulectomy typically is indicated. For those located at the urethral meatus, the Spence procedure may be warranted. With this technique, a distal diverticulum and urethral meatus are opened sharply together to form a large single meatus. Finally, for those with a complex diverticulum that may surround the urethra, a combination of techniques may be necessary.

Preoperative

PATIENT EVALUATION

Accurate information regarding diverticular anatomy is essential to surgical planning and patient counseling. For this, magnetic resonance (MR) imaging is a superior radiographic study to delineate diverticular configuration (see Fig. 26-6). Additionally, cystoscopy is valuable in locating sac openings along the urethral length.

CONSENT

With diverticular repair, damage to urethral continence mechanisms may lead to postoperative incontinence. Alternatively, urethral stricture or stenosis or urinary retention may develop depending on the extent and location of surgery. Additionally, urethrovaginal fistula and bladder injury may result. If a Spence procedure is selected, urethral meatus anatomy typically is altered, and a spraying pattern may result with urination.

PATIENT PREPARATION

To prevent wound infection, intravenous antibiotic prophylaxis is administered immediately prior to surgery (see Chap 39, Surgical Site Infection Prophylaxis). It is our practice at the University of Texas Southwestern Medical Center to recommend bowel preparation prior to diverticular repair to decompress the rectosigmoid, although this practice is not mandatory.

Intraoperative

DIVERTICULECTOMY

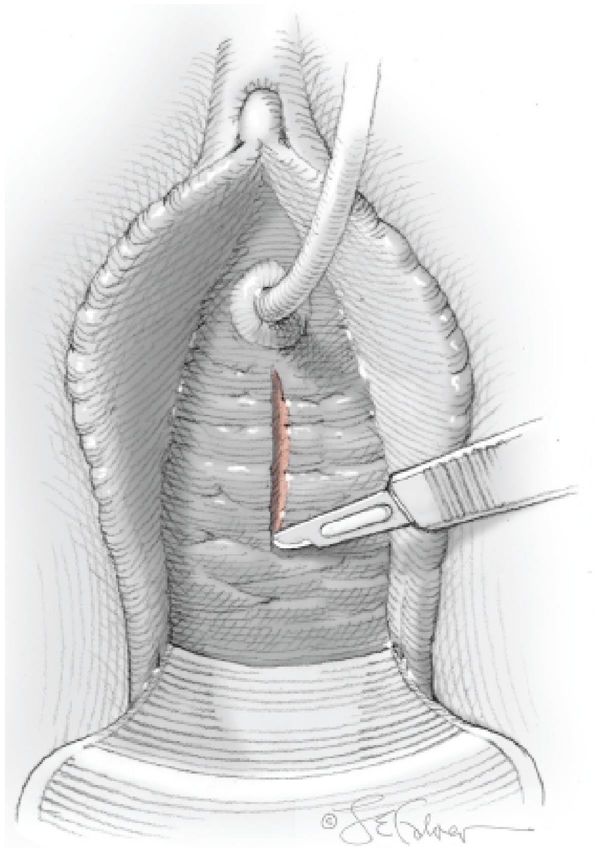
Surgical Steps

1. **Anesthesia and Patient Positioning.** Diverticulum excision typically is performed as an inpatient procedure under general or regional anesthesia. The patient is placed in high lithotomy position in candy-cane stirrups to provide maximal surgical exposure. The vagina is surgically prepared, and a Foley catheter containing a 10-mL balloon is placed in the bladder to assist in identifying the bladder neck.

2. **Cystourethroscopy.** This procedure is performed at the onset to locate the diverticular opening and exclude other abnormalities.

3. **Vaginal Incision.** A midline incision is made on the anterior vaginal wall over the diverticulum, and the vaginal epithelium is dissected sharply off the fibromuscular layer of the vaginal wall (Fig. 42-9.1). Ample epithelium is freed to allow adequate exposure and to permit tissue approximation without excess tension.

FIGURE 42-9.1

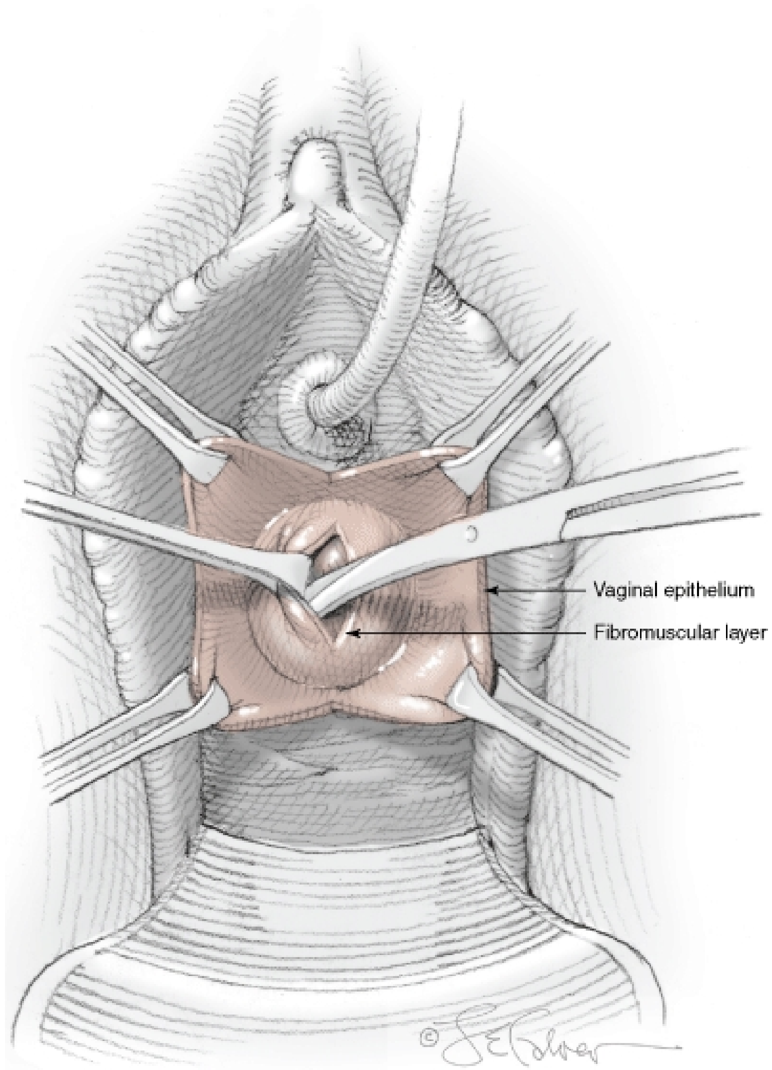


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Vaginal incision.

4. **Diverticulum Exposure.** A longitudinal incision is made through the fibromuscular layer to reach the diverticular sac. Sharp dissection then is used to completely mobilize and expose the diverticular sac and neck (Fig. 42-9.2). During dissection, the sac may be entered inadvertently or intentionally (Fig. 42-9.3). If this happens, the diverticular walls are grasped with Allis clamps, and dissection is continued. Caution and awareness of the location of the urethra are essential to avoid damage.

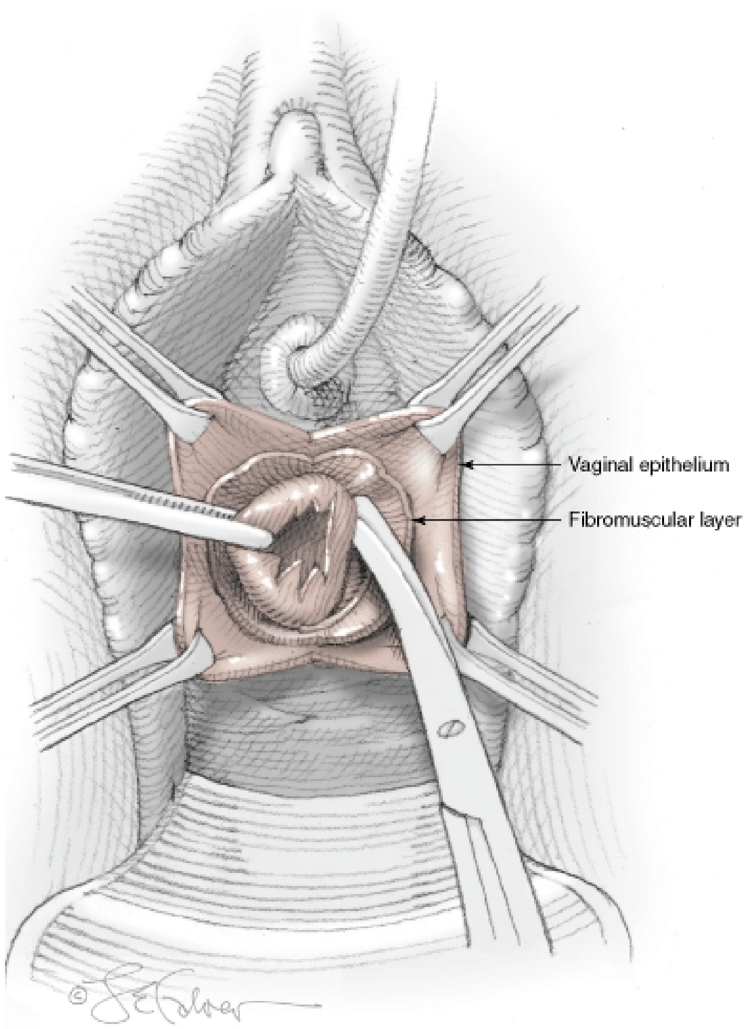
FIGURE 42-9.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Diverticular sac dissection.

FIGURE 42-9.3



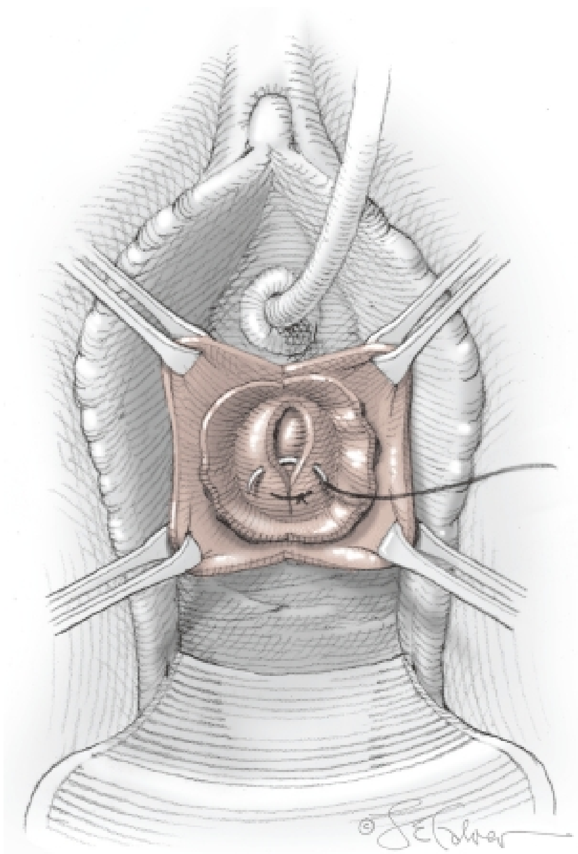
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Diverticulum excision.

5. **Diverticulum Excision.** At its neck, the diverticulum is excised from the urethra.

6. **Urethral Closure.** The urethral incision defect is closed with interrupted 4-0 delayed-absorbable sutures over the Foley catheter (Fig. 42-9.4). Fibromuscular layers are re-approximated off tension in two or more layers in a vest-over-pants fashion with 2-0 delayed-absorbable suture (Fig. 42-9.5). Redundant vaginal epithelium is trimmed, and the epithelium is closed in a running fashion with 2-0 delayed-absorbable suture.

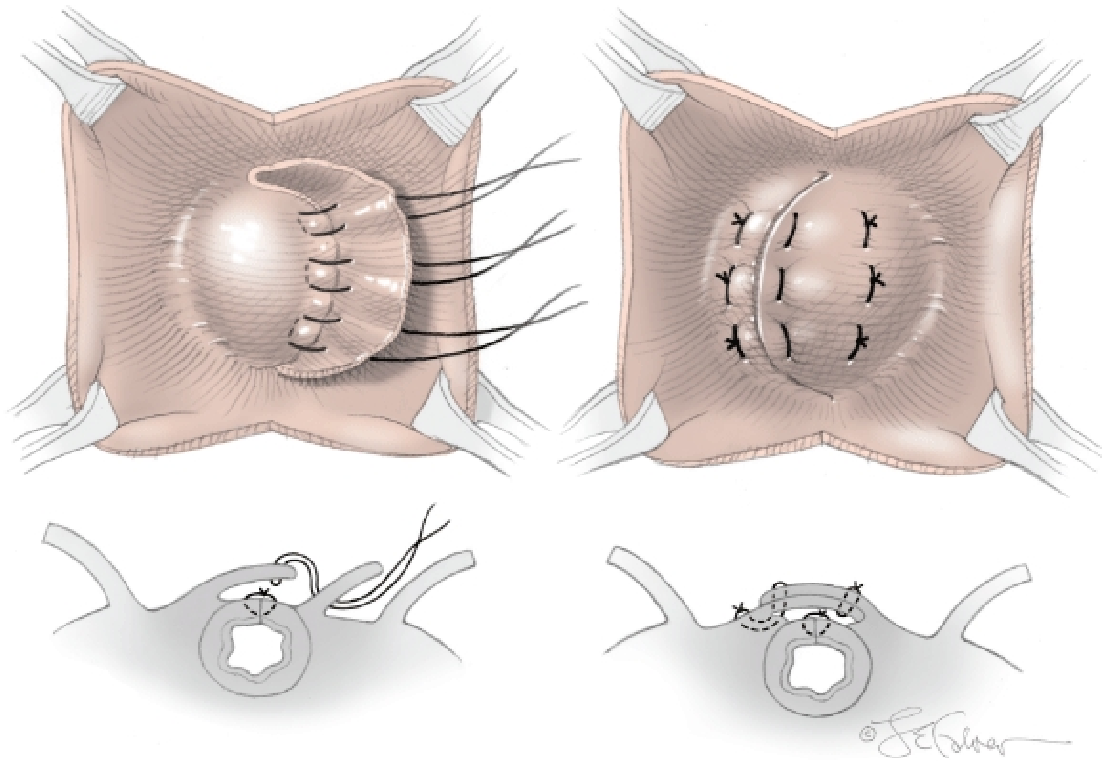
FIGURE 42-9.4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Urethral defect closure.

FIGURE 42-9.5



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Fibromuscular layer reapproximation.

PARTIAL DIVERTICULAR ABLATION

Surgical Steps

1. **Vaginal Incision.** A midline incision is made on the anterior vaginal wall over the diverticulum, and the vaginal epithelium is dissected sharply off the fibromuscular layer of the vaginal wall. Ample epithelium is freed to allow adequate exposure and later to permit defect closure off tension. The Foley catheter and balloon can be placed on gentle tension to aid in identifying the bladder and bladder neck to avoid injury.

2. **Diverticulum Exposure.** A longitudinal incision is made through the fibromuscular layer to the diverticular sac. Sharp dissection is used to completely mobilize and expose the sac. The diverticulum is opened, and the communication with the urethra is identified. To avoid injury to the proximal urethra and bladder neck, the diverticular sac, but not the neck of the diverticulum, is excised sharply. As much of the sac that can be accessed is removed.

3. **Sac Closure.** The base of the sac then is sutured side to side with 2-0 delayed-absorbable suture to cover the urethral defect. A second, and possibly a third, imbricating layer using the vaginal muscularis is created with similar suture. Excess vaginal epithelium that had previously covered the diverticulum is excised. The vaginal epithelium is closed in a running fashion with a 2-0 delayed-absorbable suture.

SPENCE MARSUPIALIZATION

Surgical Steps

1. **Meatal Incision.** Tips of Metzenbaum scissors are inserted into the urethral meatus and vagina. An incision is made through

the posterior urethral wall and entire thickness of the diverticulum and includes the distal anterior vaginal wall.

2. **Marsupialization.** A circumferential running pattern using 4-0 delayed-absorbable suture is used around the enlarged meatus to re-approximate cut edges of the vaginal and urethral epithelia.

Postoperative

Catheter management is the most important aspect of postoperative care. Although no consensus guidelines exist, most experts recommend catheter placement for 5 to 7 days. Surgeries of increasing complexity may require longer catheter duration.

42-10 VESICOVAGINAL FISTULA: LATZKO TECHNIQUE

Vesicovaginal fistulas may be repaired either vaginally or abdominally (see Chap. 26, Route of Surgical Repair). A vaginal approach is preferred for most fistulas seen in the United States, which are posthysterectomy apical fistulas. This approach is selected because of its comparable success rates, lower morbidity, and faster patient recovery. The most commonly performed vaginal procedure is the Latzko technique, which is a partial colpocleisis that obliterates the upper vagina for 2 to 3 cm around the fistula. However, an abdominal approach may be necessary for patients in whom a fistula cannot be accessed vaginally or in whom prior vaginal repairs have been unsuccessful. With the abdominal approach, omentum or peritoneum can be mobilized and interposed between the bladder and vagina to prevent recurrence.

Principles of fistula repair dictate that a repair must be performed in noninfected and noninflamed tissues. A second principle states that tissues should be approximated without excess tension. If these guidelines are followed, success rates typically are good and range from 67 to 100 percent. In the United States, most fistulas follow hysterectomy for benign causes, and these fistulas are associated with high cure rates.

Fistulas associated with gynecologic cancer and radiation therapy, however, may require adjunctive surgical procedures such as vascular flaps because these defects develop in poorly vascularized or fibrotic tissue. Even with these measures, success rates are lower.

Preoperative

PATIENT EVALUATION

Prior to repair, a fistula should be well characterized. Complex fistulas with multiple tracts or a ureterovaginal fistula should be identified. For this, proper evaluation should include intravenous pyelography (IVP) and cystoscopy (see Fig. 26-1). Ureterovaginal fistulas usually are associated with upper tract abnormalities such as hydroureter and hydronephrosis. Therefore, normal IVP findings should reassure the surgeon that ureteral involvement is absent. Additionally, this testing enables the surgeon to identify the proximity of ureters relative to a fistula for surgical planning. In general, routine posthysterectomy vesicovaginal fistulas develop at the vaginal apex. This is well away from the ureters, which enter the bladder at the level of the midvagina.

Whether or not surgery can be performed vaginally depends on the ability to obtain adequate exposure of a fistula. Therefore, during physical examination, the surgeon must assess if a fistula can be brought down into the surgical field and if a patient's pelvis affords adequate space for vaginal surgery. Some degree of prolapse of the vaginal apex is helpful for a vaginal approach to fistula repair.

Additionally, tissue infection or inflammation should be excluded. If these are identified, fistula repair should be delayed until resolution. If a fistula is recognized within a few days following hysterectomy, it may be repaired immediately, prior to a brisk inflammatory response. However, if surgical repair is not undertaken within a few days following the initial surgery, then a delay of 4 to 6 weeks is recommended to decrease tissue inflammation.

CONSENT

There is a significant recurrence rate with fistula repair, and patients should be aware that initial surgery may not be curative. With the Latzko procedure, the vagina is moderately shortened in most cases. Therefore, the risk of postoperative dyspareunia should be

included in the consent.

PATIENT PREPARATION

Bowel preparation is administered the evening prior to surgery. This decompresses the rectosigmoid and minimizes fecal contamination of the surgical field. Immediately prior to surgery, intravenous antibiotic prophylaxis commonly is administered to decrease postoperative wound infection risks.

Intraoperative

LATZKO VAGINAL REPAIR

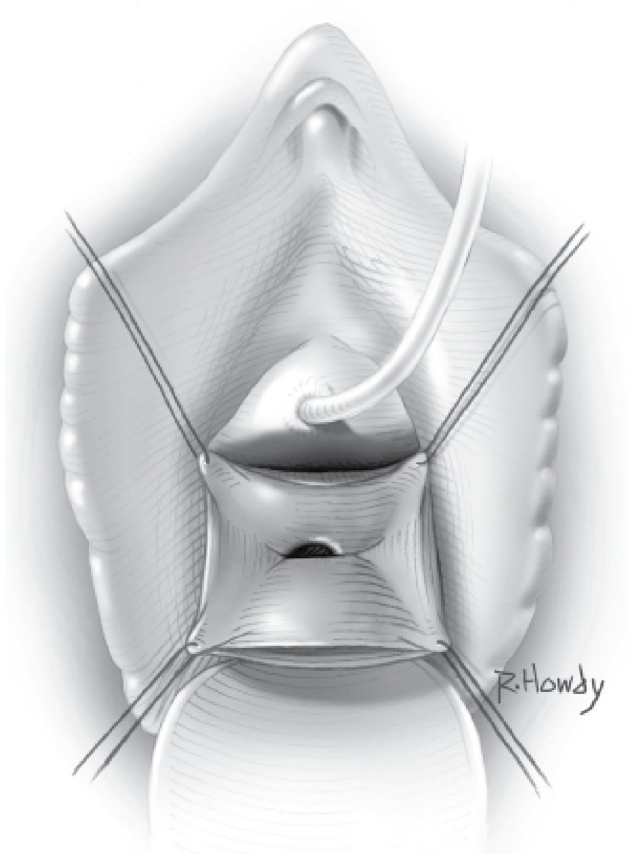
Surgical Steps

1. **Anesthesia and Patient Positioning.** In most cases, repair is performed under general or regional anesthesia, and the need for postoperative hospitalization is individualized. The patient is placed in dorsal lithotomy position, and the vagina is surgically prepared. If ureters lie close to a fistula, ureteral stents should be placed (see Section 42-1, Diagnostic and Operative Cystoscopy and Urethroscopy). Cystoscopy is required during the procedure to document ureteral patency and assess bladder integrity.

2. **Delineating a Fistulous Tract.** The course of a fistulous tract must be identified. If the tract is large enough to accept a pediatric Foley catheter, the tube is threaded through the fistulous opening, and the balloon is inflated within the bladder. If a tract cannot be delineated this manner, then lacrimal duct probes or other suitable narrow dilators should be used to trace the tract course and direction. Subsequently, attempts should be made to dilate the tract and place a pediatric catheter.

3. **Exposure.** The fistula must be brought into the operative field. If catheterization of a fistulous tract is possible, tension on the catheter will allow this. Alternatively, four sutures can be placed in the vaginal wall surrounding a fistula and used to pull the fistula into the operative field (Fig. 42-10.1). Some advocate performing a mediolateral episiotomy to gain exposure, although this is not our practice.

FIGURE 42-10.1

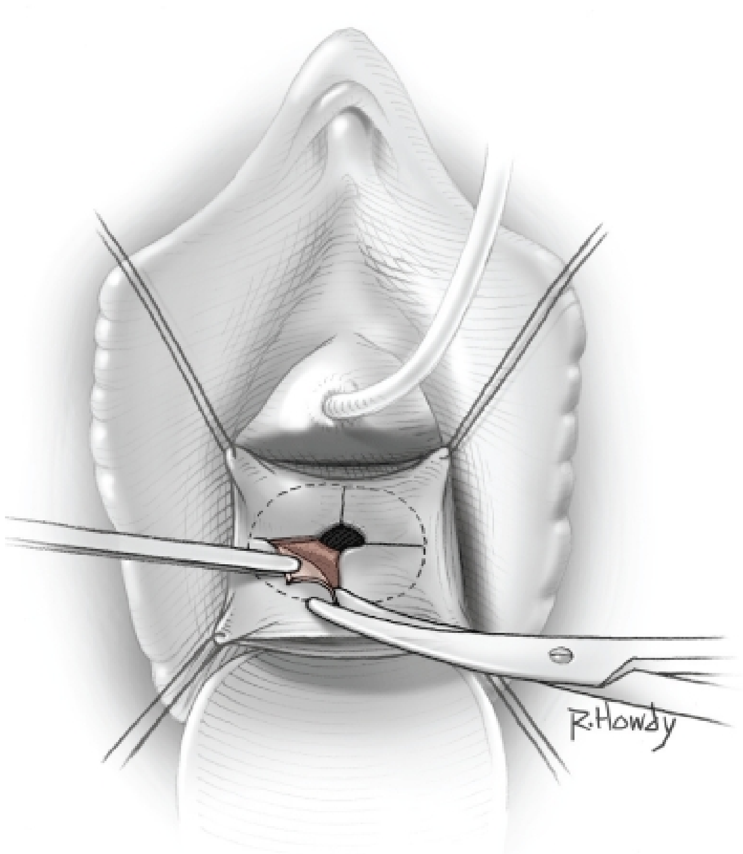


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Stay sutures in the vaginal wall improve fistula access.

4. **Vaginal Incision.** A vaginal incision is made circumferentially approximately 1 cm around the fistulous tract (Fig. 42-10.2). Vaginal mucosa surrounding the tract then is mobilized sharply and excised using Metzenbaum scissors.

FIGURE 42-10.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

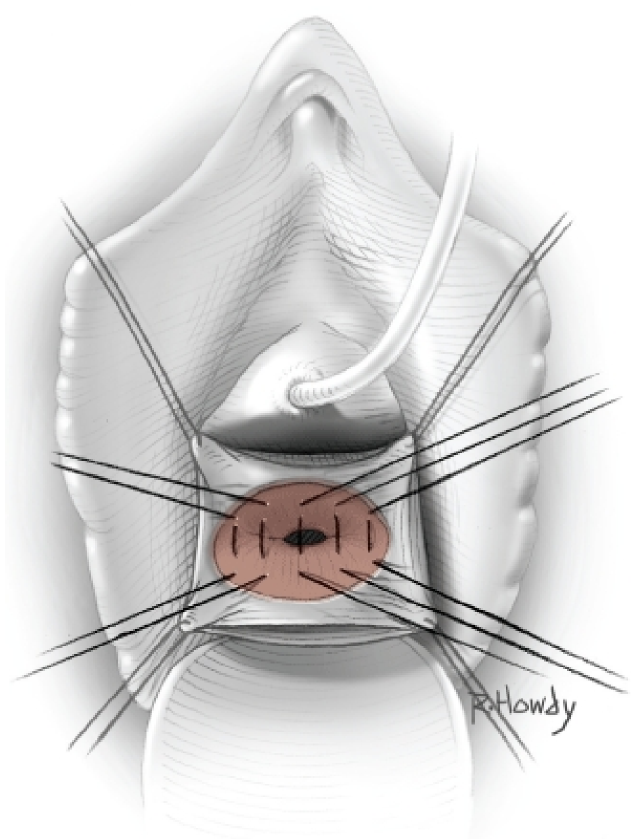
Vaginal incision.

5. **Tract Excision.** The fistula tract may or may not be excised. If the tract is excised, surgeons should be aware that a larger defect for repair will result. However, in situations in which a tract is indurated, excision is warranted.

6. **Fistula Closure.** If the tract is excised, the bladder mucosa is re-approximated with 3-0 delayed-absorbable sutures. Subsequently, anterior and posterior edges of the vaginal fibromuscular layers are approximated over this repair with interrupted stitches of 3-0 delayed-absorbable sutures (Fig. 42-10.3). After the first suture line is placed through the fibromuscular layer, a second and possibly a third line are created on top of the first (Fig. 42-10.4). Following this closure, the bladder should be filled with 100 mL of fluid to document a watertight repair. If it is not watertight, additional reinforcing sutures can be placed.

   After fibromuscular layers of the vaginal wall are closed, the epithelium is closed in a continuous running fashion using 3-0 delayed-absorbable suture.

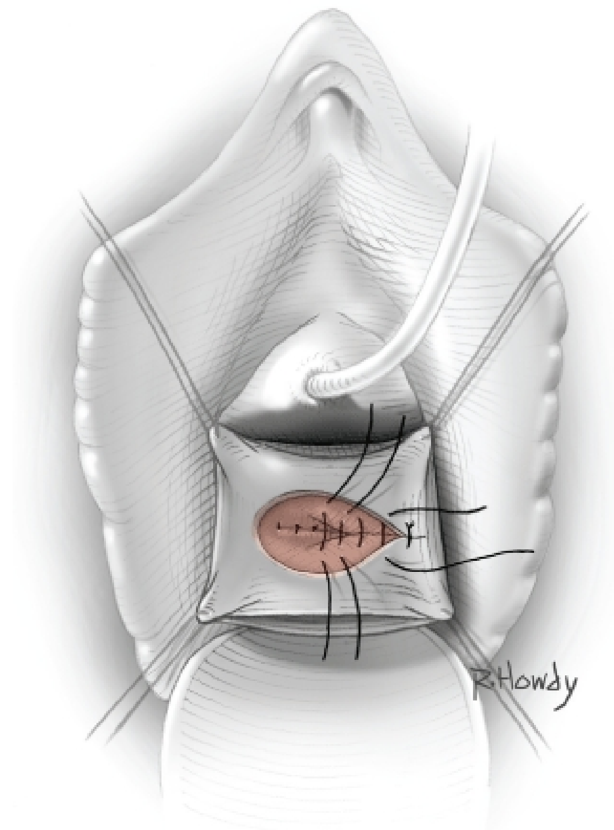
FIGURE 42-10.3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

First layer closure over fistula.

FIGURE 42-10.4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Second fibromuscular layer closure over fistula and vaginal epithelium re-approximation.

7. **Cystoscopy.** Cystoscopy is performed to document ureteral patency and to inspect the incision site.

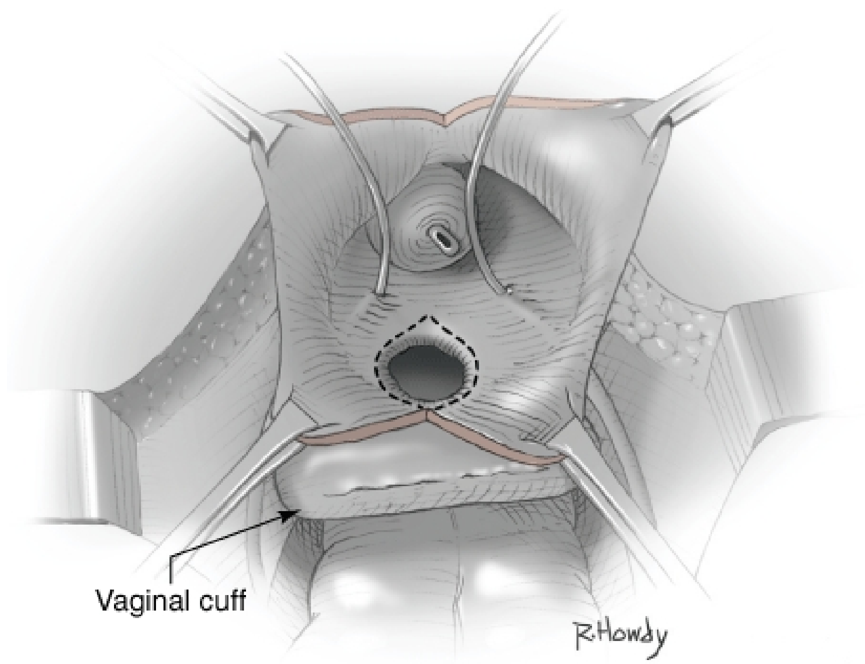
ABDOMINAL REPAIR

Surgical Steps

1. **Anesthesia and Patient Positioning.** In most cases, abdominal repair is performed under general anesthesia. The patient is placed in low lithotomy position with the use of Allen stirrups. With the patient's thighs parallel to the ground and the legs separated, access to the vagina is maximized. The abdomen and vagina are surgically prepared.

2. **Abdominal Incision and Entry into the Bladder.** A transverse or midline abdominal entry incision can be used. If mobilization of the omentum is anticipated, a midline incision may give easier access to the omentum. A Maylard or Cherney incision alternatively may be selected. After the peritoneum is entered and the upper abdomen is explored, the bowel is packed from the operating field, and a self-retaining abdominal wall retractor is placed. The space of Retzius is opened using the technique described in Section 42-2, Burch Colposuspension, and a vertical extraperitoneal incision is made in the bladder dome (Fig. 42-10.5). Correct incision placement is aided by pulling the Foley balloon to the dome or by filling the bladder with fluid.

FIGURE 42-10.5



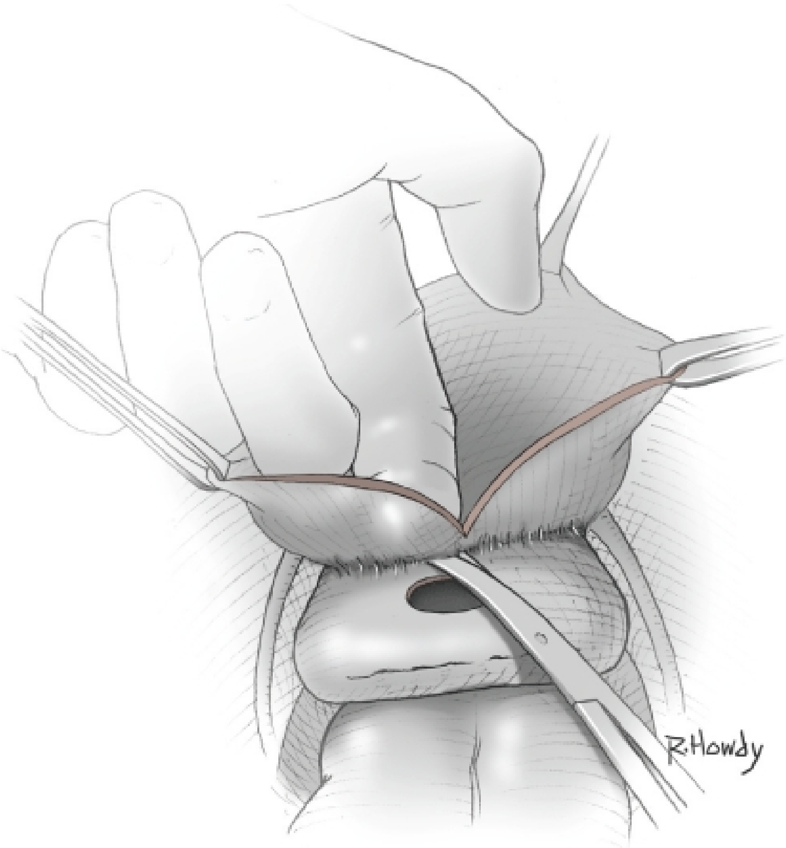
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Bladder incision.

3. **Delineation and Excision of the Fistulous Tract.** The fistula and ureteral orifices are visualized from within the bladder. If the fistula tract is near the orifices, ureteral stents are placed. The incision then is extended over the top and back of the bladder to the fistula tract. A lacrimal probe or catheter may be placed into the fistula tract to delineate its course. The tract then is excised.

4. **Separation of the Bladder and Vagina.** Sharp dissection is used to dissect the vagina away from the bladder in the area of the fistula (Fig. 42-10.6). Scarring may be extensive, and sharp rather than blunt dissection should be used. To aid dissection, an EEA sizer may be placed in the vagina for manipulation. The vagina should be separated widely from the bladder to allow omentum placement between the two organs.

FIGURE 42-10.6

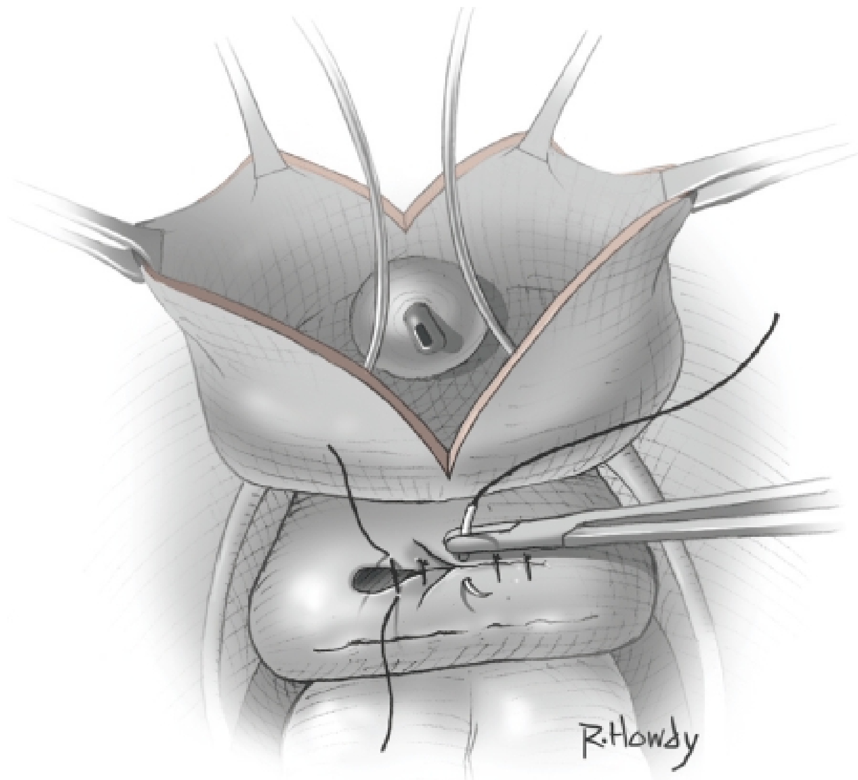


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Separation of the bladder and vagina.

5. **Vaginal Closure.** The vagina is closed in two layers with 2-0 delayed-absorbable suture (Fig. 42-10.7). The end-to-end anastomosis (EEA) sizer or digital manipulation of the vagina will assist this closure (see Fig. 42-17.5).

FIGURE 42-10.7

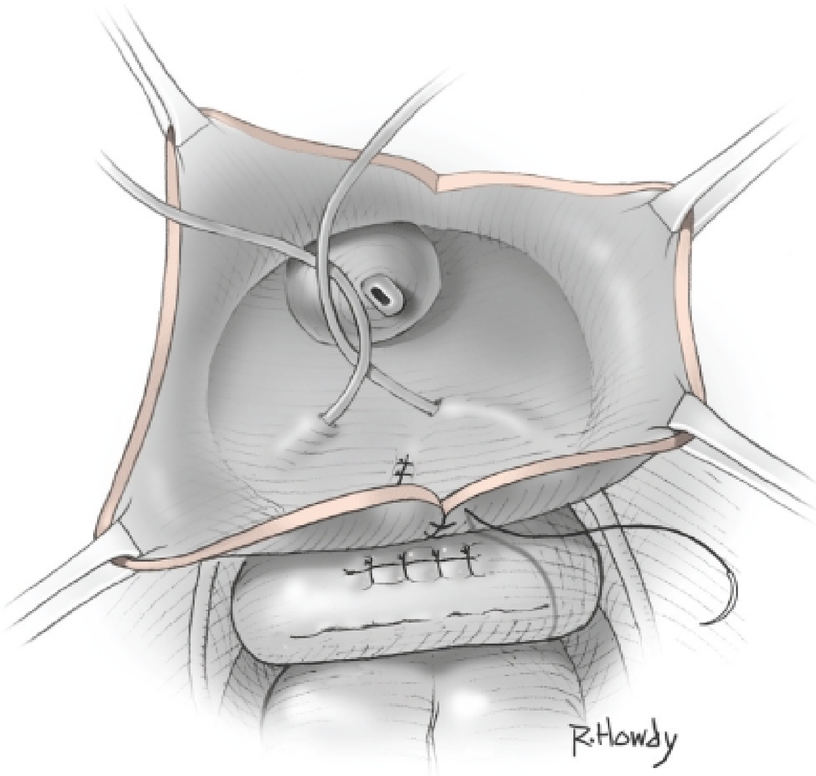


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Vaginal closure.

6. **Bladder Closure.** The bladder is closed in two layers using running sutures of 3-0 absorbable suture (Fig. 42-10.8). The second layer should be imbricated such that the first suture line is covered and tension is released (Fig. 42-10.9).

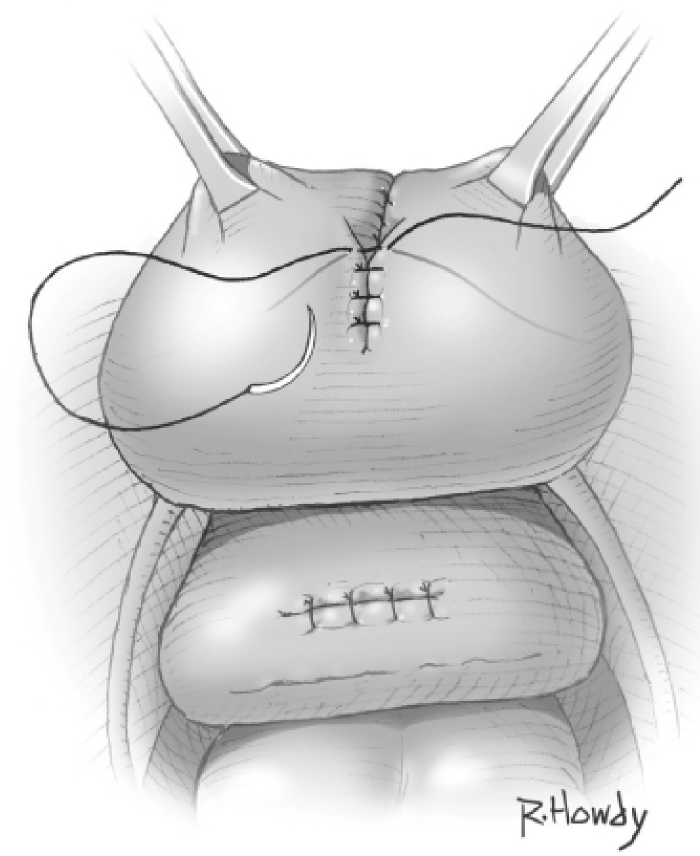
FIGURE 42-10.8



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

First layer bladder closure.

FIGURE 42-10.9

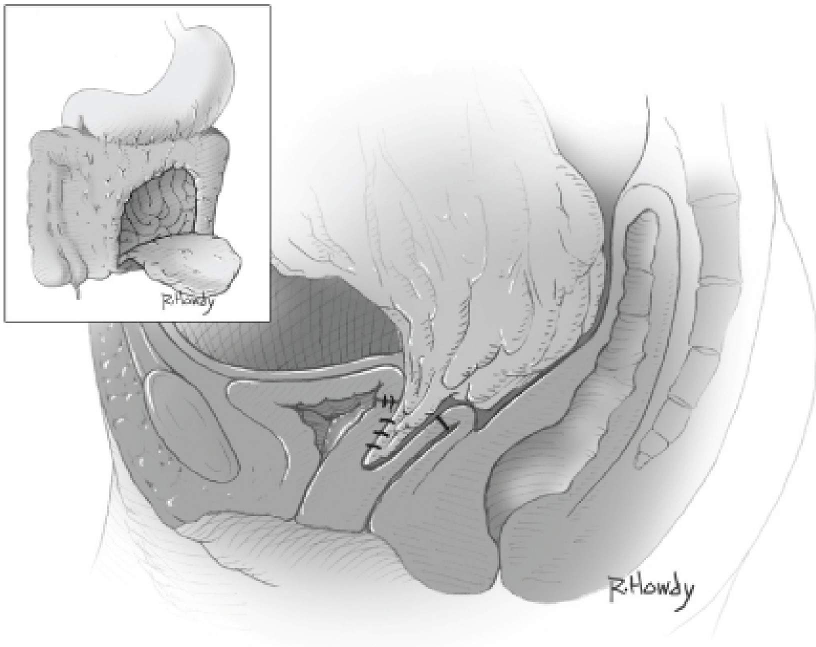


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Second layer bladder closure.

7. **Omental or Peritoneal Interposition.** The omentum is mobilized and sutured to the anterior wall of the vagina to cover the incision line (Fig. 42-10.10). This provides a tissue layer between vagina and bladder, increases vascular flow to the area, and may improve tissue healing. Alternatively, if the omentum cannot be mobilized, peritoneum may be interposed between the bladder and vagina (Fig. 42-10.11).

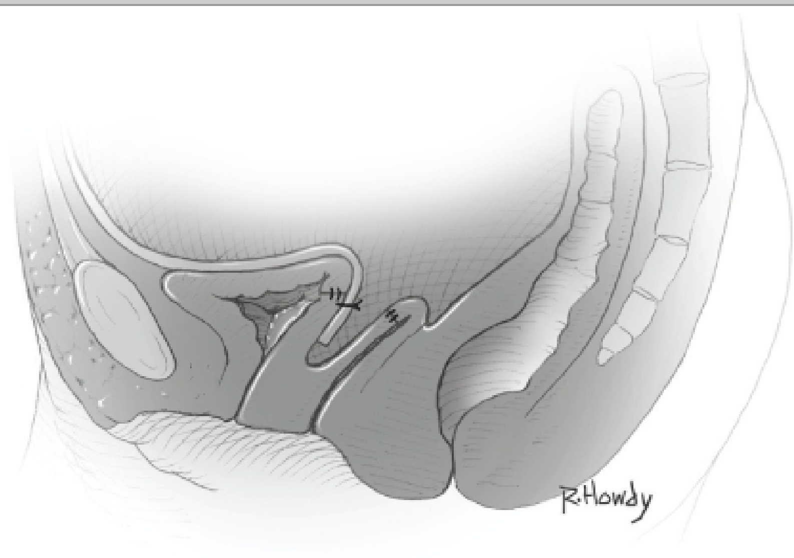
FIGURE 42-10.10



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Peritoneal interposition.

FIGURE 42-10.11



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Peritoneal interposition.

8. **Cystoscopy.** Cystoscopy is performed to document ureteral patency and to inspect the incision site.

9. **Incision Closure.** The abdominal incision is closed as described in Sections 41-1, Midline Vertical Incision or 41-2, Pfannenstiel Incision.

Postoperative

The bladder should be drained postoperatively to prevent overdistention and suture disruption. Transurethral and suprapubic catheter placement will ensure adequate drainage in the immediate postoperative period. At our institution, we generally continue catheterization for at least 3 weeks following vesicovaginal fistula repair.

42-11 MARTIUS BULBOCAVERNOSUS FAT PAD FLAP

The Martius bulbocavernosus fat pad flap is a vascular graft. It is used commonly in complex rectovaginal or vesicovaginal fistula repairs complicated by avascular or fibrotic tissue. Specifically, previously irradiated vaginal tissues often require this graft.

During graft placement, the bulbocavernosus fat pad is first mobilized and subsequently brought to the fistula site through a vaginal incision. By means of this graft, fistula repair layers receive additional vascular support to increase rates of successful wound healing.

Preoperative

PATIENT EVALUATION

In most instances, graft placement is anticipated for those with prior radiation or with fistula recurrence. Therefore, preoperative planning includes assessment of tissue vascularity, connective tissue strength, and ability to mobilize vaginal tissues adequately to create a multilayered fistula closure. To undergo this procedure, a woman must have adequate labial fat, and this should be assessed prior to surgery.

CONSENT

The consenting process for this procedure includes that for the primary fistula repair. Additionally, women are informed of the potential for postoperative vulvar dysesthesia, pain, or hematoma.

PATIENT PREPARATION

Preoperative bowel preparation is indicated prior to use of a Martius flap to repair rectovaginal fistulas. Preparation protocols vary according to surgeon preference and may include administration of oral cathartic solutions, laxatives, or enemas (see Table 39-10). Because of the risk of poor wound healing in these complicated fistulas, antibiotic prophylaxis with a first- or second-generation cephalosporin is warranted (see Table 39-7).

Intraoperative

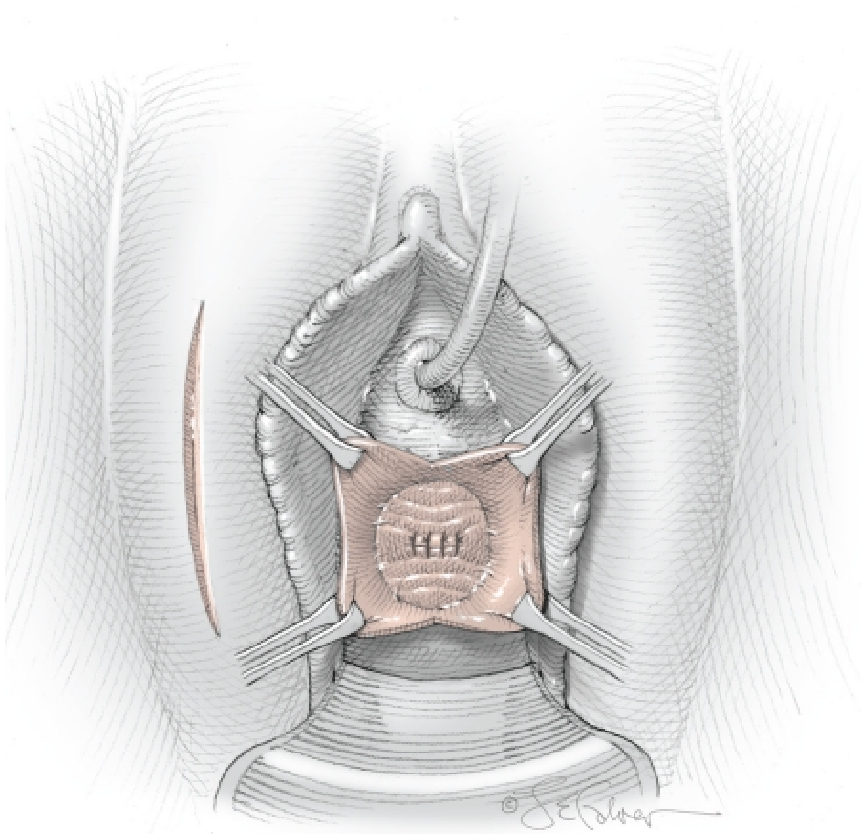
Surgical Steps

1. **Anesthesia and Patient Positioning.** In most cases, a Martius flap graft and fistula repair can be performed with general or regional anesthesia, and the need for postoperative hospitalization typically is individualized. The patient is positioned in high lithotomy position, the vagina is surgically prepared, and a Foley catheter is placed.

2. **Fistula Repair.** Rectovaginal or vesicovaginal fistulas are repaired as outlined in Sections 42-10, Vesicovaginal Fistula: Latzko Technique and 42-26, Rectovaginal Fistula Repair.

3. **Labial Incision.** After completion of fistula repair, the lateral margin of one labia majora is incised (Fig. 42-11.1). The length of the incision is tailored to specific labial anatomy and size of the graft needed. In many cases, a 6- to 8-cm incision is made below the level of the clitoris and is extended inferiorly.

FIGURE 42-11.1

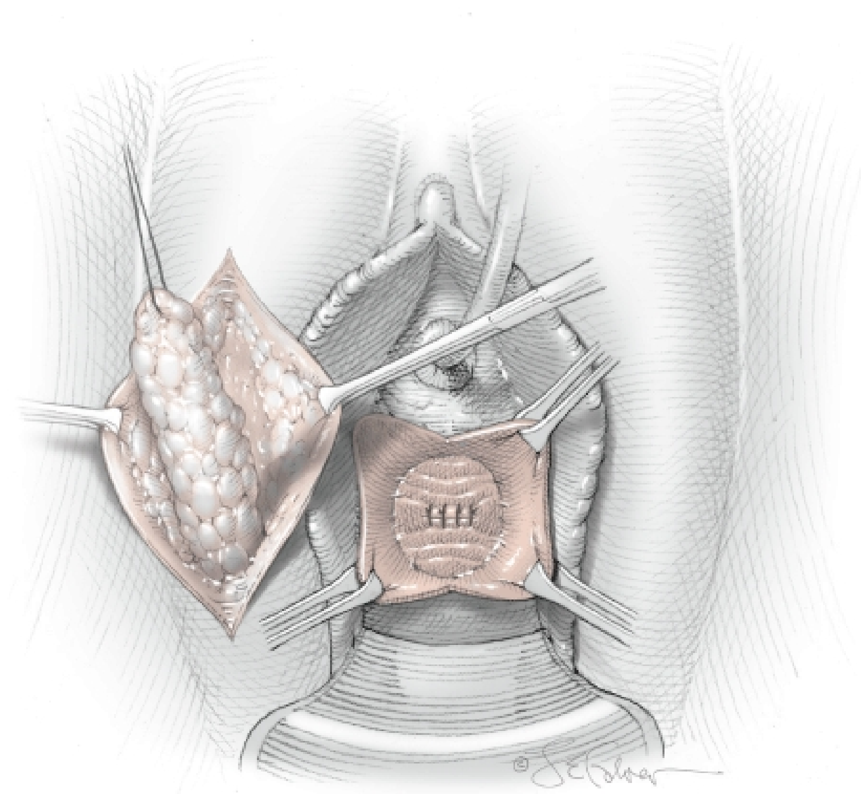


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Labial incision.

4. **Mobilization of the Fat Pad.** Incision edges are retracted laterally, and sharp dissection is used to mobilize the bulbocavernosus fat pad (Fig. 42-11.2). This tissue is vascular, and vessels ideally are ligated prior to transection. A broad base is left inferiorly, and the fat pad is detached superiorly.

FIGURE 42-11.2

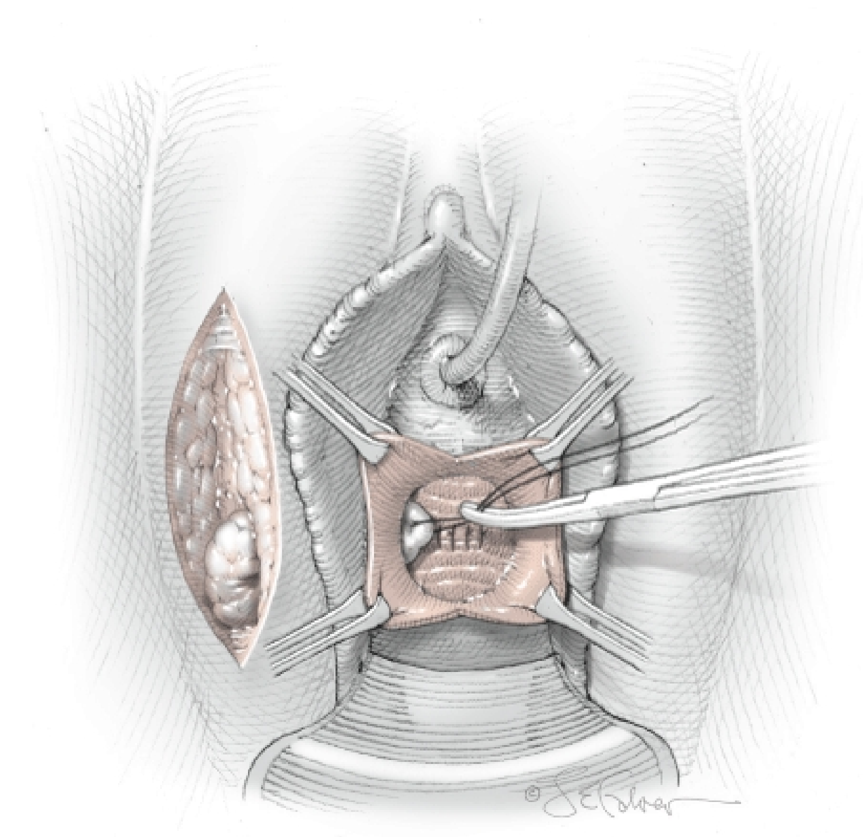


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Mobilization of the fat pad.

5. **Graft Placement.** After mobilization, a tunnel is created by bluntly dissecting with a hemostat from the vulvar incision underneath the vaginal epithelium to the fistula site. The tunnel must be of sufficient breadth to avoid vascular compression and resulting graft necrosis. A suture is placed at the graft tip and is used to pass the graft through the tunnel and into the vagina (Fig. 42-11.3).

FIGURE 42-11.3

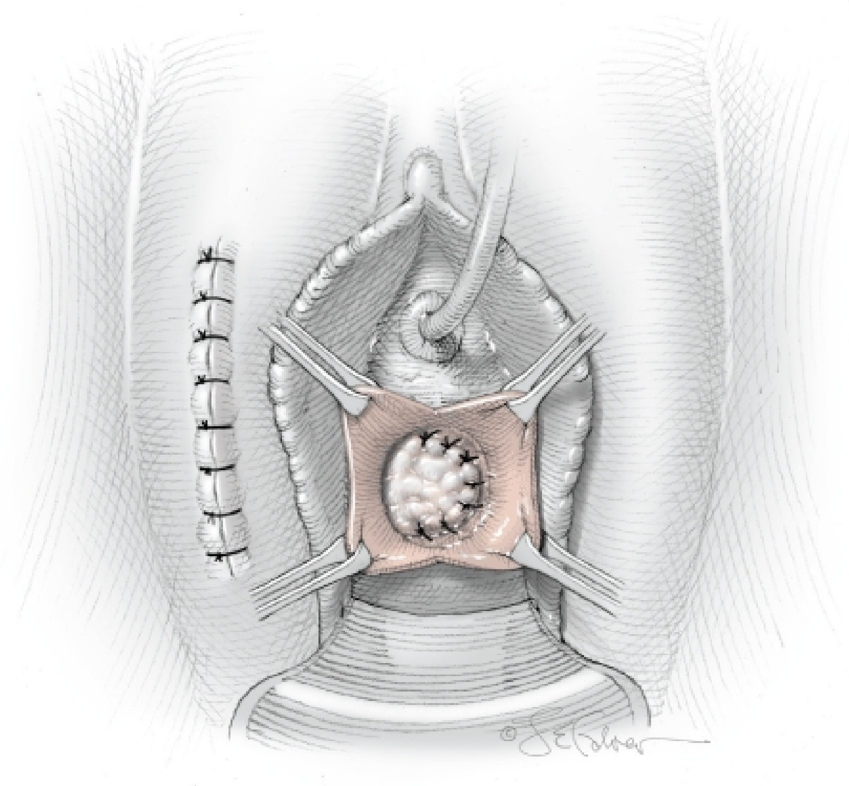


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Graft placement.

6. **Graft Fixation.** The graft is secured to the vaginal muscularis overlying the fistula repair with several interrupted stitches using 3-0 delayed-absorbable suture (Fig. 42-11.4).

FIGURE 42-11.4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Graft fixation.

7. **Incision Closure.** The vulvar incision is re-approximated along its length with interrupted subcuticular closure using 3-0 delayed-absorbable suture. The vaginal mucosa overlying the fistula is closed with a continuous running technique using 3-0 delayed-absorbable suture.

Postoperative

Care after surgery is dictated predominantly by the associated fistula repair. However, sitz baths twice daily typically are added to improve pain and healing of the vulvar incision.

42-12 SACRAL NEUROMODULATION

Sacral neuromodulation is a technique that delivers electrical stimulation to the pelvic plexus and pudendal nerves. This device is a Food and Drug Administration (FDA)â€"approved treatment for urinary urgency, frequency, urge incontinence, and for nonobstructive urinary retention. Although not FDA approved for pelvic pain and interstitial cystitis, it is sometimes used for these indications if they are associated with urgency, frequency, or retention. This surgery typically is performed for women who have failed to improve adequately from multiple other conservative therapies. The mechanism of action is unclear, but it is believed to modulate reflex pathways involved in bladder storage and emptying and innervation of the pelvic floor.

Sacral neuromodulation generally is completed in two steps. In the first stage, a lead is placed into the sacrum and connected to an external stimulus generator via an extension device. A test stimulation period of approximately 2 weeks follows. If symptoms are

decreased by 50 percent over the next several weeks, then a long-term use implantable pulse generator (IPG) is placed in the superior buttock fat in a second surgical procedure.

Preoperative

PATIENT EVALUATION

Prior to surgery, women should have completed a full evaluation, including urodynamic testing, voiding diary, cystoscopy, and other selected tests.

CONSENT

After the first stage, a 50-percent improvement in symptoms is considered a benchmark of success. Approximately, 75 percent of patients achieve this level of improvement and are candidates for IPG placement. Common complications following stage one include lack of clinical response or infection. For those who undergo second-stage implantation, approximately 80 percent reach the improvement benchmark and have greater than 50-percent improvement in symptoms.

Following the second stage, pain at the IPG site, infection, and lack of clinical response are common complications. After sacral neuromodulation, magnetic resonance (MR) imaging and security wanding at airport security checkpoints are contraindicated.

Intraoperative

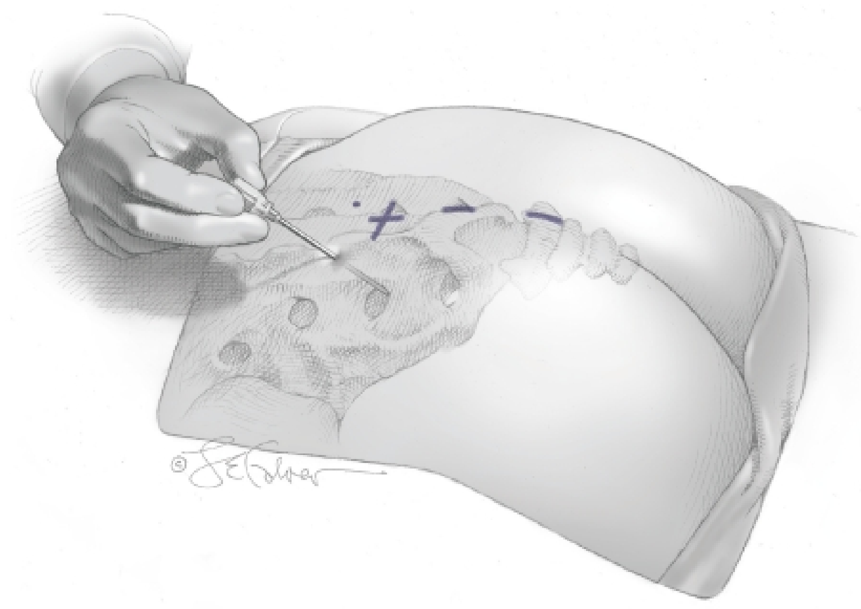
Surgical Steps

1. **Anesthesia and Patient Positioning.** Prior to surgery, antibiotics are administered. The patient is positioned prone on a Wilson frame or with a pillow under the abdomen and knees. The buttocks are separated to allow visualization of anus and perineum. General anesthesia is required to protect the airway, but neuromuscular blockade is contraindicated because this will prohibit neuromuscular stimulation evaluation. The sacrum and perianal areas are surgically prepared. A Foley catheter typically is not required because of the surgery's brevity.

2. **Identification of S3 Foramina.** These landmarks are the site of lead placement and are located approximately 9 cm above the coccyx and 1 to 2 cm lateral to the midline. Foramina are outlined with a surgical marker. A foramen needle is placed horizontally at the suspected level of S3, and a confirmatory fluoroscopic image is obtained.

3. **Foramen Needle Insertion.** The needle is inserted into the skin above the foramina and is guided at a 60-degree angle caudally into the opening (Fig. 42-12.1). If possible, the lead is placed concordant with patient handedness. Pelvic floor reflexes are checked, and when appropriate S3 reflexes are obtained, lead placement is initiated.

FIGURE 42-12.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

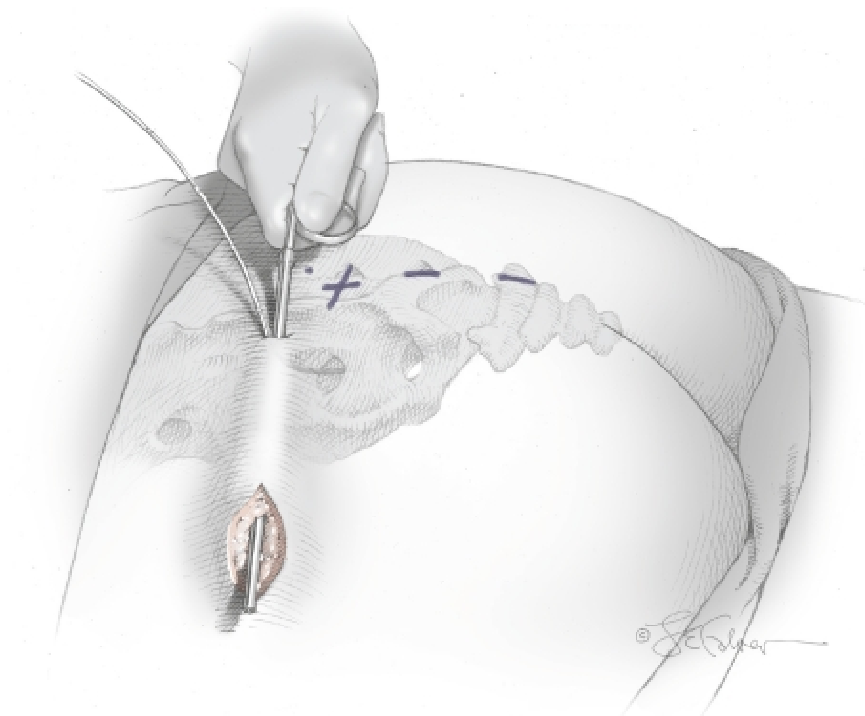
Foramen needle insertion.

4. **Lead Placement.** A guidewire is placed down the foramen needle under fluoroscopic guidance. The needle then is removed, and a small stab incision is made at the point where the guidewire enters the skin. A lead introducer then is passed over the guidewire into the foramina, again under fluoroscopic guidance. The guidewire is removed. With continued fluoroscopy, the tined lead then is passed down the introducer into the appropriate position at the S3 foramina. All four electrodes on the lead are tested for S3 pelvic floor reflexes, and after the lead is positioned correctly, the lead introducer is removed. The tines lock into place within the foramina when the trocar is removed. Thus, the leads cannot be repositioned after this point.

5. **Pulse Generator Incision and Lead Passage.** A 4- to 6-cm incision is made over the lateral buttock. Sharp and blunt dissection is used to create a deep pocket that can house the percutaneous lead extension for the temporary external pulse generator and eventually the permanent IPG. The pocket should be deep enough into the subcutaneous tissue that it does not indent the skin, but it should not sit directly above the muscle.

   After a pocket is created, a tunneling device is used to feed the lead from the midline incision into the pocket (Fig. 42-12.2).

FIGURE 42-12.2



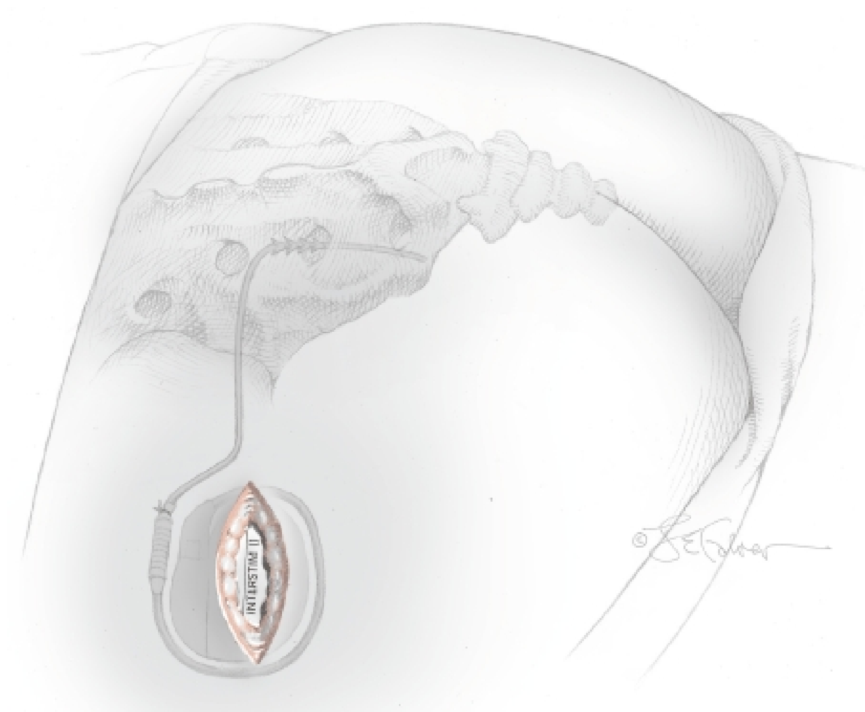
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Pulse generator incision and lead passage.

6. **Placement of the Percutaneous Lead Extension (First Stage).** Extending from the S3 foramina, the lead is connected to the percutaneous lead extension. A stab incision then is created lateral to the pocket, and the tunneling device is used to guide the percutaneous lead extension through the pocket and out the stab incision. The subcutaneous tissue then is closed over the connector with 2-0 delayed-absorbable suture in a running fashion. The skin is closed with a subcuticular stitch using 4-0 delayed-absorbable suture and dermabond. The percutaneous lead extension is connected to a temporary external pulse generator, which is used for 1 to 4 weeks to assess neuromodulation efficacy.

7. **Implantable Pulse Generator Placement (Second Stage).** If significant relief of symptoms is obtained, the permanent IPG is placed 1 to 4 weeks after the initial surgery. The procedure is performed with the patient prone and usually with general anesthesia for airway control. The lateral incision is opened down to the percutaneous lead extension, and the previously created pocket is re-opened. The connector and percutaneous lead extension are removed, and the permanent IPG is connected directly to the lead (Fig. 42-12.3). The incision is closed as step 6.

FIGURE 42-12.3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Implantable pulse generator placement.

Postoperative

Pain or erythema at the incision site suggests cellulitis, abscess, or seroma. These symptoms should be evaluated as soon as possible, with institution of antibiotics if needed. Unusual pain also should be evaluated immediately because this could suggest lead malfunction. A woman can turn the device off by herself if necessary.

Symptoms are continually assessed postoperatively, and the IPG is reprogrammed as needed. Reprogramming the device or changing leads often can improve refractory symptoms.

42-13 ANTERIOR COLPORRHAPHY

Anterior colporrhaphy is one of the more commonly performed gynecologic surgeries. Although it is still used as a primary choice for repair of anterior vaginal wall prolapse (cystocele), randomized trials suggest that anatomic cure is obtained in 50 percent of patients or less (Weber, 2001). Therefore, several different techniques are used to augment traditional anterior colporrhaphy, including vaginal paravaginal defect repair (PVDR) and re-inforcement with synthetic or biologic mesh.

During traditional anterior colporrhaphy procedure (midline plication), attenuated supporting connective tissue between the vagina and bladder is reapproximated and reinforced using plication sutures. This bolstering along the length of the vagina attempts to elevate the bladder and urethra to a more anterior and anatomically normal position. The vaginal PVDR attempts to provide lateral support to the anterior vaginal wall. Mesh augmentation procedures may be used to add tissue strength and provide lateral and midline support.

In observational series, success rates for mesh augmentation range from 93 to 100 percent after 2 years (Julian, 1996; Mage, 1999; Migliari, 1999). In randomized studies, however, rates of improvement in excess of those found with with traditional colporrhaphy are more modest, approximating 15 percent (Sand, 2001; Weber, 2001). Additionally, the associated risks of mesh

erosion and infection should be factored into any decision to add reinforcing mesh (Cervigni, 2001). Cadaveric fascia has been used similarly. Gandhi (2005), however, found no improved rates of surgical success using this material.

In women with cystocele, other points of pelvic support also may require concurrent repair. Accordingly, anterior colporrhaphy is performed frequently in combination with corrective surgeries for enterocele, rectocele, and vaginal apex prolapse.

Preoperative

PATIENT EVALUATION

Women with anterior vaginal wall prolapse commonly have associated stress urinary incontinence (SUI) (Borstad, 1989). Even those who are continent, however, may have SUI unmasked following anterior vaginal wall prolapse correction. Thus, preoperative urodynamic evaluation is recommended. During this evaluation, the prolapse is reduced to its anticipated postoperative position to mimic pelvic floor dynamics following surgery (Chaikin, 2000; Yamada, 2001). The decision to perform a concurrent prophylactic anti-incontinence procedure then is dictated by individual urodynamic findings.

CONSENT

For most women, anterior colporrhaphy has low rates of complications. Of these, recurrence of the anterior vaginal wall defect is one of the most common. Several factors have been noted to increase this risk and include a large original defect and an increased number of other prolapsed pelvic compartments. In addition to prolapse recurrence, postoperative dyspareunia has been noted. Less frequently, serious hemorrhage or cystotomy may complicate this procedure. If mesh is used, erosion or extrusion is a risk.

PATIENT PREPARATION

To decompress the rectum and thereby increase operating space within the vagina, bowel preparation typically is administered the evening prior to surgery. Antibiotic prophylaxis with a first- or second-generation cephalosporin is recommended immediately prior to surgery.

Intraoperative

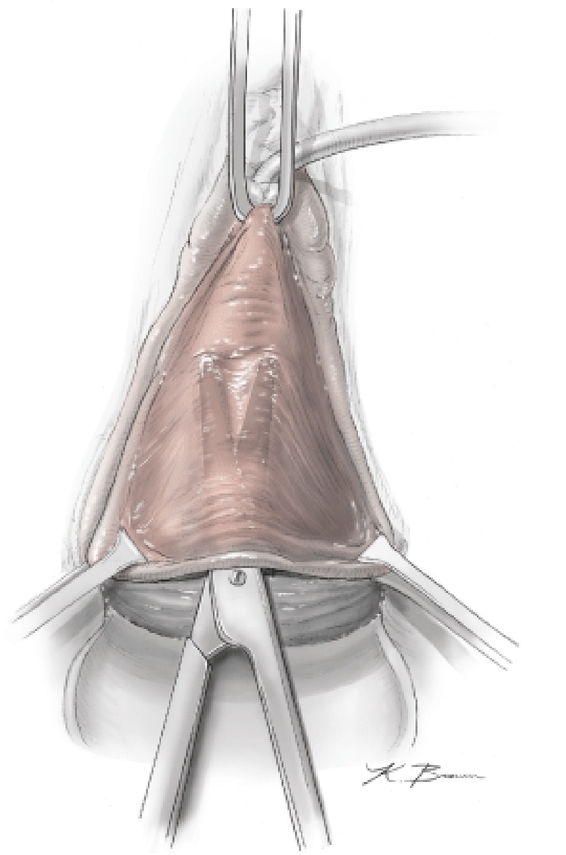
Surgical Steps

1. **Anesthesia and Patient Positioning.** After adequate general or regional anesthesia is administered, the patient is placed in the dorsal lithotomy position, the vagina is surgically prepared, and a Foley catheter is placed. An Auvard weighted speculum is positioned to retract the posterior vaginal wall.

2. **Concurrent Surgery.** If other reconstructive surgeries are required, they may precede or follow anterior colporrhaphy. Anterior colporrhaphy may be performed with the uterus in situ or alternatively, completed following hysterectomy.

3. **Vaginal Incision.** One to 2 cm distal to the vaginal apex, an Allis clamp is placed on each side of the anterior vaginal wall (Fig. 42-13.1). These clamps are gently pulled laterally to create tension, and the vaginal wall between them is incised transversely. Following incision, a third clamp is placed in the midline 3 to 4 cm distal to this incision (Fig. 42-13.1). All three clamps are held, creating gentle outward tension.

FIGURE 42-13.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

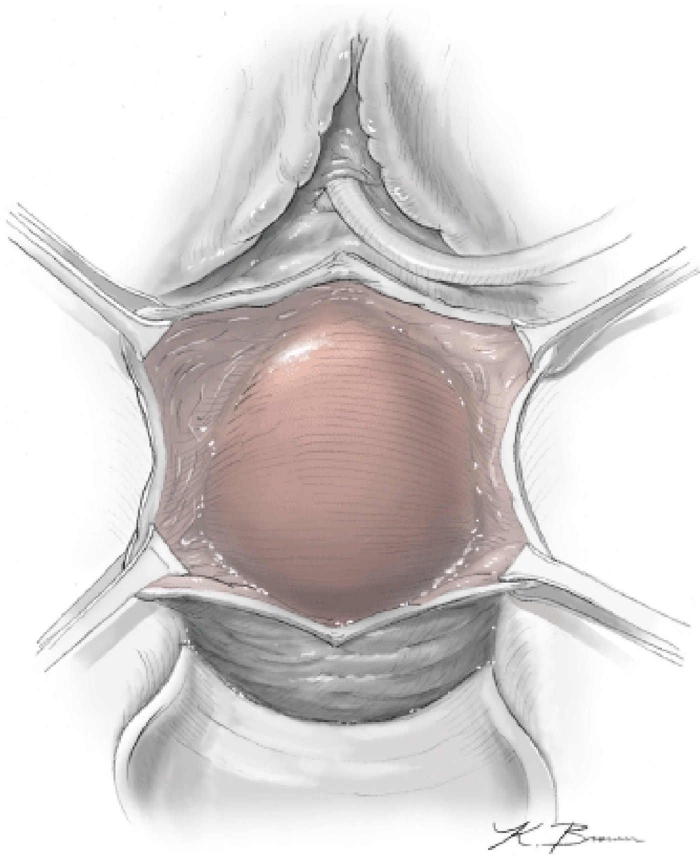
Tissue plane dissection.

4. **Tissue Plane Dissection.** The tips of curved Metzenbaum scissors are insinuated beneath the vaginal mucosa. Opening and closing the scissor blades while exerting gentle forward pressure within the plane underlying the vaginal mucosa allows separation from the fibromuscular layer (Fig. 42-13.1). This dissection continues distally to reach the midline Allis clamp. The undermined vaginal wall then is incised longitudinally.

   Additional Allis clamps are placed, one on each freed mucosal edge. The more distal central Allis clamp is moved 3 to 4 cm further distally. The steps of vaginal wall dissection then are repeated. This process continues until the wall has been bisected and dissected to within 2 to 3 cm of the urethral meatus. This ending spot corresponds to a midpoint along the length of the urethra.

   The lateral attachments of the vaginal wall to the underlying fibromuscular layer are separated next. Allis clamps are placed on the cut vaginal edges and fanned laterally to create tension (Fig. 42-13.2). With one finger behind the vaginal wall, the scissors are held parallel to the wall, and the epithelial layer is dissected sharply from the fibromuscular layer (Fig. 42-13.3). A combination of sharp and blunt dissection is used, and once the proper tissue plane is entered, the layers separate readily. This dissection is extended laterally and almost reaches the pubic rami.

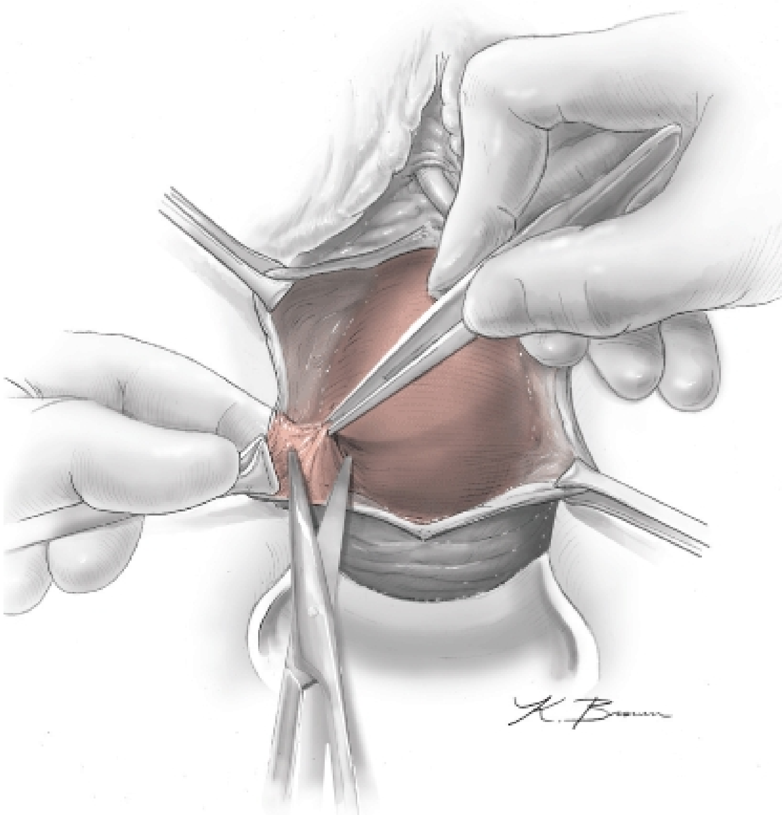
FIGURE 42-13.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Vaginal incision.

FIGURE 42-13.3

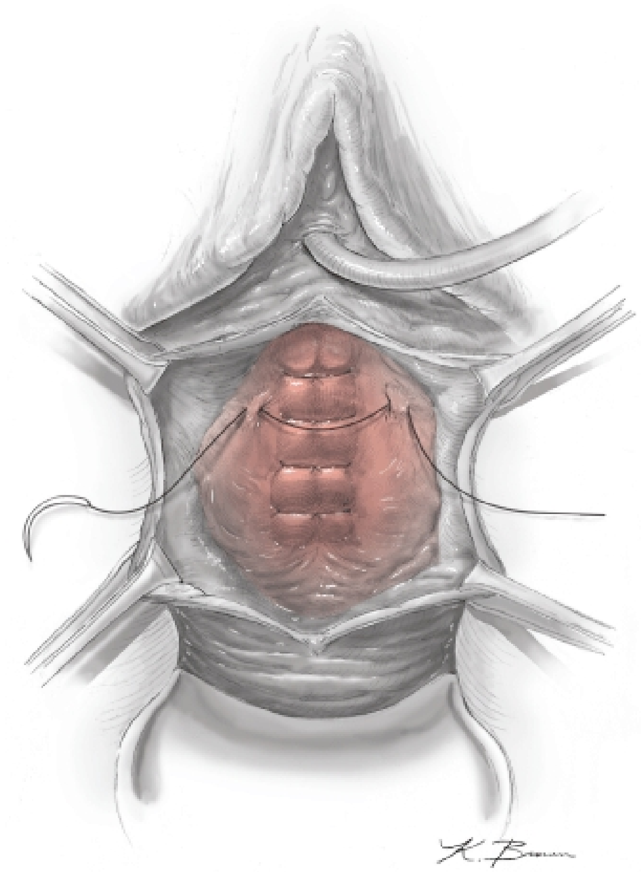


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Separation of mucosa and fibromuscular layer.

5. **Traditional Anterior Coloporrhapy (Midline Plication).** Plication of the fibromuscular layer then is begun. Interrupted sutures of 2-0 permanent or delayed-absorbable suture on an SH needle are placed in the midline along the length of the vaginal wall (Fig. 42-13.4). Plication of the fibromuscular layer creates a double layer of support for the bladder and urethra. Tissue tension should create a firm shelf overlying the bladder, but extreme tension is avoided to prevent sutures from pulling through the fascia or excessively narrowing the vagina. As sutures are tied, the bladder is pushed by the surgeon gently upward and away from the incision line. A second layer of plication sutures is placed beginning lateral to the first, if necessary (Fig. 42-13.4).

FIGURE 42-13.4



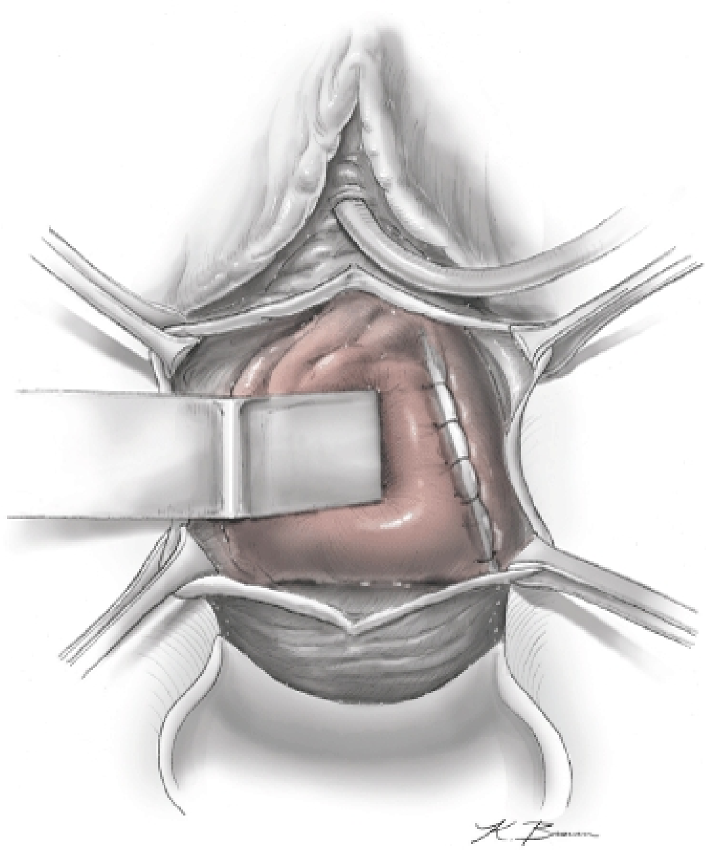
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Midline plication.

6. **Vaginal Paravaginal Defect Repair.** For women with anterolateral vaginal wall defects, vaginal PVDR may be used primarily. If PVDR is to be performed, lateral dissection proceeds along the ischipubic rami from the pubic symphysis to the ischial spine. Blunt dissection is used to enter the space of Retzius. If a paravaginal defect is present, the space is entered easily. The arcus tendineus fascia pelvis is seen as a white line running from the ischial spine to the symphysis. Visualization is aided with the use of Breisky-Navratil and lighted retractors (see Fig. 40-20).

   A series of four to six 0-gauge permanent sutures are placed in the arcus tendineus or obturator fascia and attached to the lateral edge of the vaginal fibromuscular layer (Fig. 42-13.5). This is then repeated on the other side. If necessary a midline plication can be performed after the vaginal paravaginal sutures are tied, however, the vagina wall should not be placed on tension.

FIGURE 42-13.5

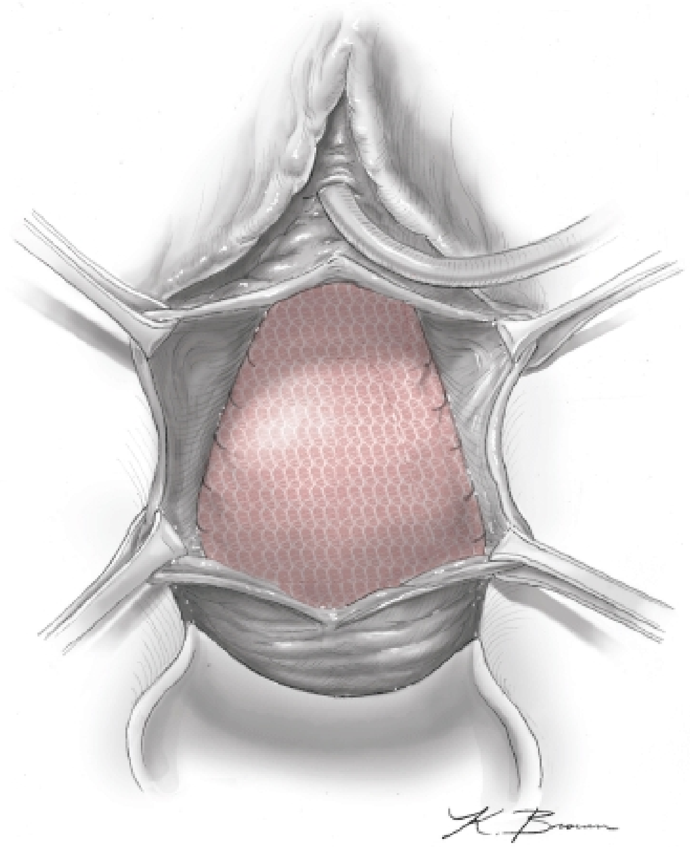


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Vaginal paravaginal defect repair.

7. **Mesh Augmentation.** For the mesh augmentation procedure, dissection proceeds similar to that for the PVDR. The mesh is cut in a trapezoidal shape and is attached to the arcus tendineus with four 2-0 permanent sutures on each side (Fig. 42-13.6). Mesh augmentation may be used solely to re-inforce an anterior wall defect or may be used after midline plication, as described earlier (step 5).

FIGURE 42-13.6

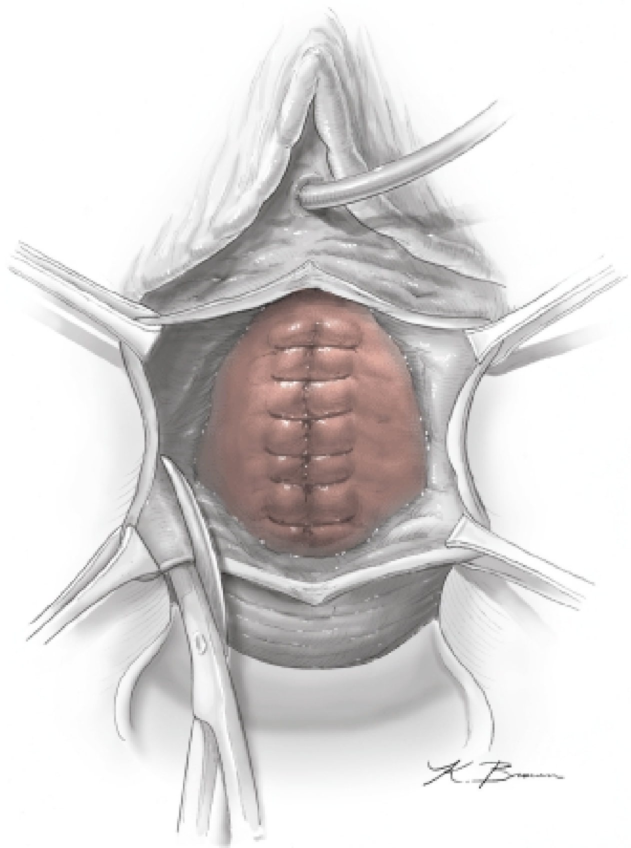


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Mesh final placement.

8. **Incision Closure.** Depending on the size of the original cystocele, some redundant vaginal wall likely will be present and require trimming (Fig. 42-13.7). Liberal trimming, however, can place the vaginal wall incision on excessive tension, affect wound healing, and narrow the vagina. Therefore, care should be taken to minimized tissue excision. The vaginal mucosa is re-approximated using a running suture with a 2-0 delayed-absorbable suture.

FIGURE 42-13.7



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Second layer of plication and excess mucosa trimmed.

9. **Cystoscopy.** Kwon and colleagues (2002) performed cystoscopy following 346 anterior colporrhaphy procedures and found unexpected injury in 2 percent of patients. These each required suture removal and replacement. Accordingly, cystoscopy may be warranted to document the integrity of the ureteral orifices, bladder, and urethral lumen.

Postoperative

Recovery following anterior colporrhaphy for most women is rapid and associated with few complications. Urinary retention or urinary tract infection, however, is common. In anticipation of retention, many surgeons advocate bladder drainage until urine residuals fall below 200 mL.

As with other vaginal surgery, diet and activity can be advanced as tolerated. Women, however, should abstain from intercourse until complete wound healing, typically at 6 to 8 weeks following repair.

42-14 ABDOMINAL PARAVAGINAL DEFECT REPAIR

Paravaginal defect repair (PVDR) is a prolapse procedure that corrects lateral defects in the anterior vaginal wall. The procedure involves attachment of the lateral vaginal wall to the arcus tendineus fascia pelvis (see Fig. 38-25). Over the last 20 years, PVDR has become popular as we have gained a deeper understanding of the importance of lateral defects in anterior vaginal wall

prolapse pathophysiology.

Paravaginal defect repair is primarily a prolapse operation and has not been shown to be an effective treatment for stress urinary incontinence (SUI). This repair can be performed alone or in combination with other prolapse procedures. For example, PVDR frequently is performed in conjunction with the Burch procedure (see Section 42-2, Burch Colposuspension). Paravaginal defect repair provides support to the middle and upper vagina, whereas the Burch procedure provides middle and distal support.

Paravaginal defect repair also can be performed laparoscopically by those with advanced laparoscopic skills. If sutures can be placed the same as in the abdominal approach, the results are expected to be equivalent.

Preoperative

PATIENT EVALUATION

Demonstration of lateral vaginal wall defects on physical examination is required prior to surgery. These are outlined in Chapter 24, Visual Descriptors. If significant anterior wall prolapse is identified, evaluation for SUI or potential SUI should be pursued. In women who have an isolated paravaginal defect, there is the risk that other pelvic support defects such as apical or posterior vaginal prolapse may develop. Thus, attempts to identify these potential defects should precede surgery. In some instances, prophylactic repair of potential defects is indicated.

CONSENT

Paravaginal defect repair provides effective support to the lateral vaginal walls, but as with other prolapse procedures, long-term success rates diminish with time. The procedure involves surgery in the space of Retzius, which has the potential for significant blood loss. In particular, those who have had prior surgery in this space are at increased risk of significant hemorrhage. Inaccurate suture placement can result in injury to the bladder and/or ureters, although this is uncommon, especially in the hand of an experienced surgeon. Additional complications include postoperative urinary incontinence or retention.

PATIENT PREPARATION

To prevent wound infection, antibiotic prophylaxis is given (see Chap. 39, Surgical Site Infection Prophylaxis). It is our practice to recommend bowel preparation prior to PVDR to decompress the bowel, although this practice is not mandatory. However, if this procedure is performed in combination with more extensive pelvic reconstructive surgeries, then thorough bowel evacuation is warranted (see Table 39-10).

Intraoperative

Surgical Steps

1. **Anesthesia and Patient Positioning.** This surgery typically is performed as an inpatient procedure under general or regional anesthesia. Following administration of anesthesia, the patient should be positioned in low lithotomy using Allen stirrups. Adequate exposure to the vagina is vital because a vaginal hand is used to elevate and dissect the paravaginal space. The abdomen and vagina are surgically prepared, and Foley catheter with a 10-mL balloon is placed.

2. **Abdominal Incision.** A low transverse incision placed 1 cm superior to the symphysis pubis affords the best exposure to the space of Retzius (see Section 41-2, Pfannenstiel Incision). Entry into the peritoneal cavity is not necessary, however, this may assist in placement of a self-retaining retractor.

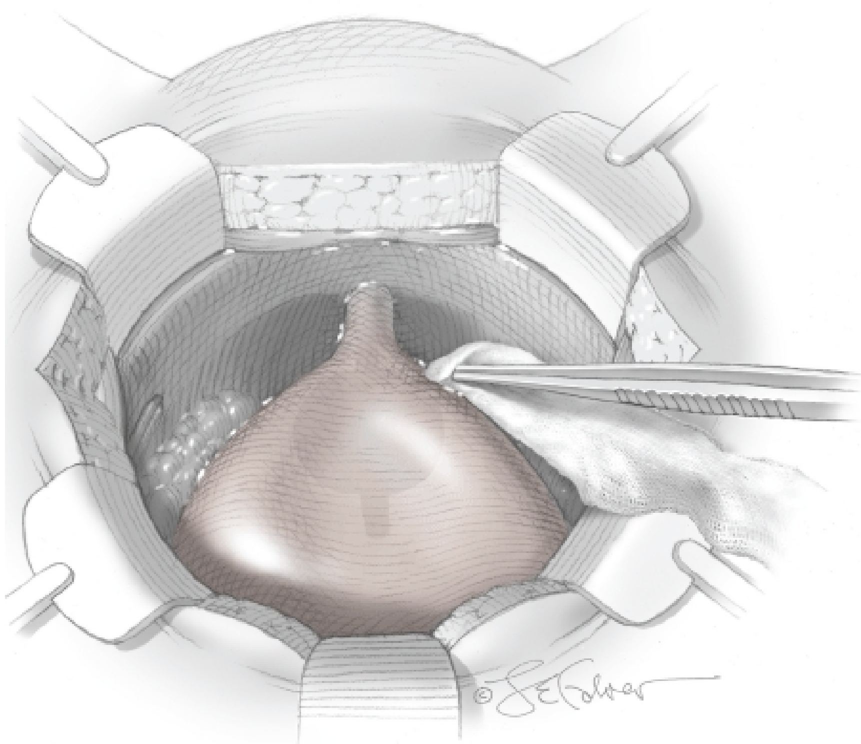
3. **Entering the Space of Retzius.** After incision of the fascia, the rectus muscles are separated in the midline, and retractors are used to hold them in apposition. Careful dissection of this space decreases the risk of hemorrhage and creates accurate tissue planes for suture placement. The correct plane of dissection for opening the space of Retzius is directly behind the pubic bone. Loose areolar tissue is dissected gently in a mediolateral fashion with fingers or sponge beginning immediately behind the pubic bone (Fig. 42-14.1). If the correct plane is entered, this avascular potential space opens easily and without significant hemorrhage. If bleeding does occur, it is likely that the wrong tissue plane had been entered.

   After the medial portion of the space of Retzius is opened, the obturator canal should be palpated bilaterally so that the vessels and nerve within this area can be avoided (see Fig. 38-25). The ischial spine then is palpated 4 to 5 cm directly below

the obturator canal. The remainder of the paravaginal space is opened with gentle finger dissection or gentle insertion of 4 x 4 in gauze sponges into the lateral paravaginal spaces. This is aided by a vaginal hand pushing up into the space.

Large paravaginal blood vessels are noted along the lateral vaginal wall. Bleeding of these vessels is controlled easily by upward pressure of the vaginal hand while hemostatic sutures are placed.

FIGURE 42-14.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

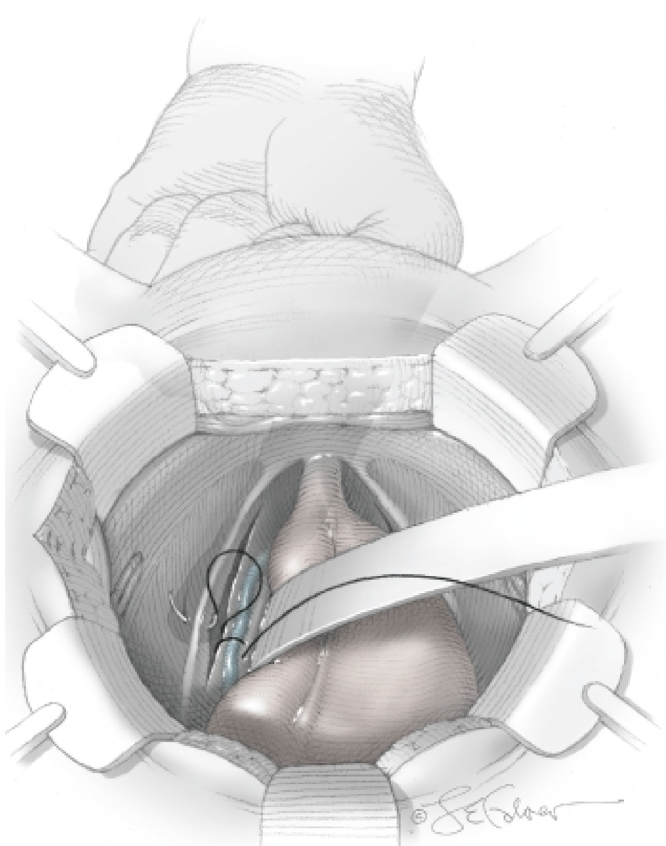
Dissection in the space of Retzius.

4. **Identification of the Arcus Tendineus Fascia Pelvis.** The arcus tendineus fascia pelvis runs between the pubic symphysis and the ischial spine (see Fig. 38-25). It is observed in this location along the sidewall as a condensation of white connective tissue. In those with defects, it may be torn in the middle or completely avulsed from the sidewall.

5. **Placement of Paravaginal Sutures.** With a hand in the vagina pressing upward into the paravaginal space, a medium-sized malleable retractor is used to reflect the bladder medially and protect it from inadvertent suture placement.

   The most cephalad suture is the first one placed (Fig. 42-14.2). The vaginal finger presses upward, against the lateral vaginal wall, and a figure-of-eight stitch with 2-0 permanent suture is placed around the paravaginal vessels, taking care to avoid entry into the vaginal lumen. If bleeding follows, the suture is tied to constrict involved vessels. The suture then is placed through the arcus tendeneus fascia pelvis at a point 1 to 2 cm caudal to the ischial spine. Sutures are not tied until all paravaginal sutures have been placed. During suture placement, the obturator canal and neurovascular bundle should be visualized and avoided. Three to five more paravaginal stitches then are placed at 1-cm intervals until the level of the bladder neck is reached (Fig. 42-14.3). After all sutures are placed, they are tied, and the procedure is repeated on the other side of the vagina.

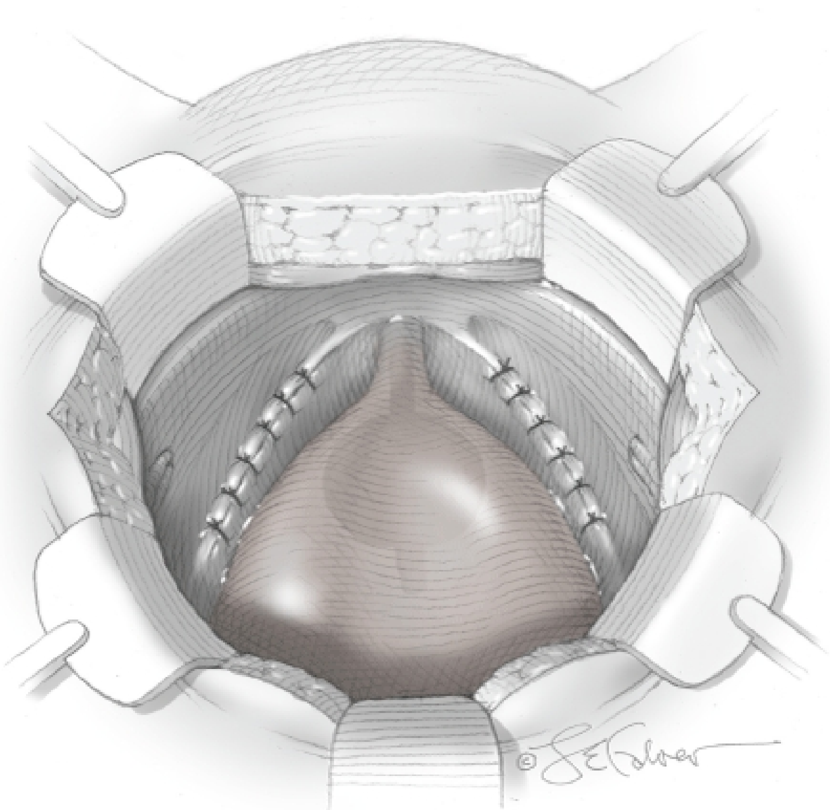
FIGURE 42-14.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Placement of paravaginal sutures.

FIGURE 42-14.3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Final suture placement.

6. **Cystoscopy.** One half to 1 ampule of intravenous indigo carmine is administered intravenously, and cystoscopy is performed. Efflux from both ureteral orifices must be seen. In addition, the bladder surfaces should be inspected for sutures. A misplaced suture might be seen as a dimple in the bladder wall. If found, sutures entering the bladder should be removed and replaced properly.

7. **Incision Closure.** After vigorous irrigation of the space of Retzius, the abdomen is closed in a standard fashion (see Section 41-2, Pfannenstiel Incision). If the peritoneum was opened, closure is recommended to prevent small bowel adhesions in the space of Retzius.

8. **Concurrent Procedures.** In patients with stress urinary incontinence, a Burch procedure might be performed after placement of paravaginal sutures. In this case, cystoscopy is delayed until after the Burch procedure is completed.

Postoperative

In general, recovery follows that associated with laparotomy and varies depending on concurrent surgeries and incision size. A voiding trial as described in Chapter 39, Voiding Trials is performed prior to hospital discharge.

42-15 POSTERIOR COLPORRHAPHY

Posterior colporrhaphy traditionally is used to repair prolapse of the posterior vaginal wall (rectocele). Specifically, posterior

colporrhaphy techniques attempt to re-inforce the fibromuscular layer of tissue between the vagina and rectum to prevent prolapse of the rectum into the vaginal lumen.

In many situations, the apex of the posterior vaginal wall also must be suspended to obtain successful repair. Thus, if care is not given to apical descent, recurrent prolapse may follow. Additionally, perineorrhaphy often is carried out in conjunction with posterior colporrhaphy.

Variations of posterior colporrhaphy have been developed to improve success rates. Current methods include midline plication, defect-directed repair, and placement of re-inforcing materials. Evidence, however, does not indicate that one of these is more effective.

Preoperative

PATIENT EVALUATION

A detailed discussion of symptoms should begin every patient evaluation prior to colporrhaphy. Often patients may associate all their bowel symptoms to the presence of a posterior wall bulge, but the two may not be related. Specifically, if constipation is a major complaint, then a trial of nonsurgical treatment may be warranted. Symptoms most likely to be to cured by this procedure include the need to digitally decompress the rectal vault and the sensation of vaginal bulge.

Posterior wall prolapse commonly accompanies other support defects, and women should undergo a complete pelvic organ prolapse examination, as described in Chapter 24, Perineal Examination. If concurrent anterior vaginal wall or vaginal apical prolapse is present, this also should be repaired.

CONSENT

In addition to standard surgical risks, this procedure may be associated with failure to correct symptoms or anatomy. Therefore, a patient and surgeon should identify treatment goals and discuss expectations. In the few randomized studies that have been done, current techniques give a less than optimal anatomic repair, and success rates approximate 70 percent. An additional common risk includes dyspareunia. However, injury to the rectum is rare.

PATIENT PREPARATION

A thorough bowel preparation is indicated to prevent fecal contamination during surgery. Additionally, delay of immediate postoperative defecation may be beneficial for patient comfort and can be achieved with a clear-liquid or low-residual diet. Antibiotic prophylaxis with a first- or second-generation cephalosporin is recommended.

Intraoperative

Surgical Steps

1. **Anesthesia and Patient Positioning.** Posterior colporrhaphy typically is an inpatient procedure performed under general or regional anesthesia. A patient is place in high lithotomy position with stirrups of the surgeon's choosing, and the vagina is surgically prepared. A Foley catheter is not needed unless required by concurrent surgeries.

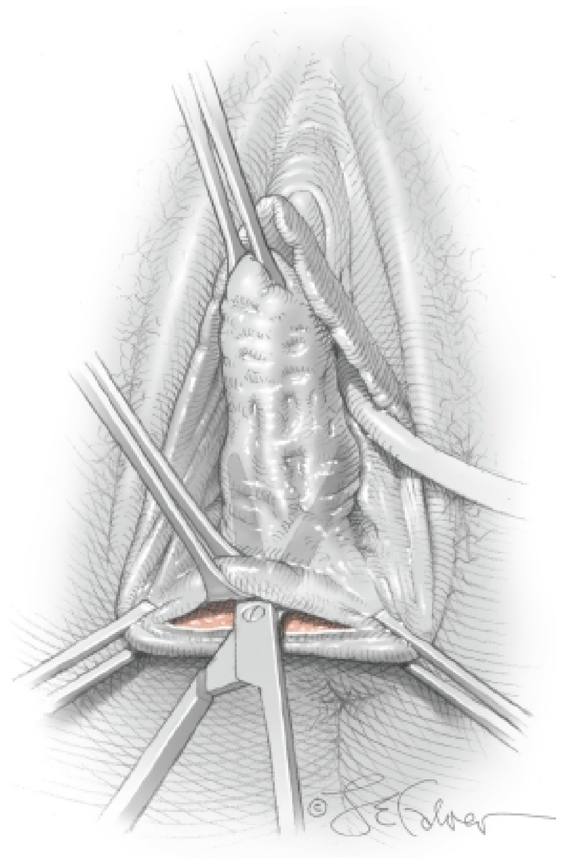
2. **Vaginal Incision and Dissection.** Corners of the introitus are grasped with Allis clamps. A third Allis clamp is placed in the vaginal midline at the proximal apex of the vaginal bulge. At the perineum, a horizontal incision is made and extended between the Allis clamps at the introitus.

   Metzenbaum scissors then are used to develop the incision by undermining the vaginal mucosa (Fig. 42-15.1). Because of fusion of the fibromuscular layer within the perineal body, as well as possible scarring from prior episiotomy, clear tissue planes are not present. Thus, in the area immediately adjacent to the perineal body, sharp dissection is required. Once the vaginal mucosa is reached, however, clear tissue planes typically are encountered, and blunt dissection can be combined with sharp dissection.

   During dissection, care should be taken to stay in the correct tissue plane. Deep dissection can lead to entry into the rectum, whereas superficial dissection can create defects in the vaginal mucosa, often called *button holes.* Dissection should extend cephalad to the level of the proximal Allis clamp previously placed at the apex.

A midline vertical incision then is made from the perineal incision to the apex using Metzenbaum scissors. The edges of the midline incision are grasped with Allis clamps. Additional bilateral sharp and blunt dissection typically is necessary to further separate the fibromuscular layer from the vaginal epithelium laterally.

FIGURE 42-15.1

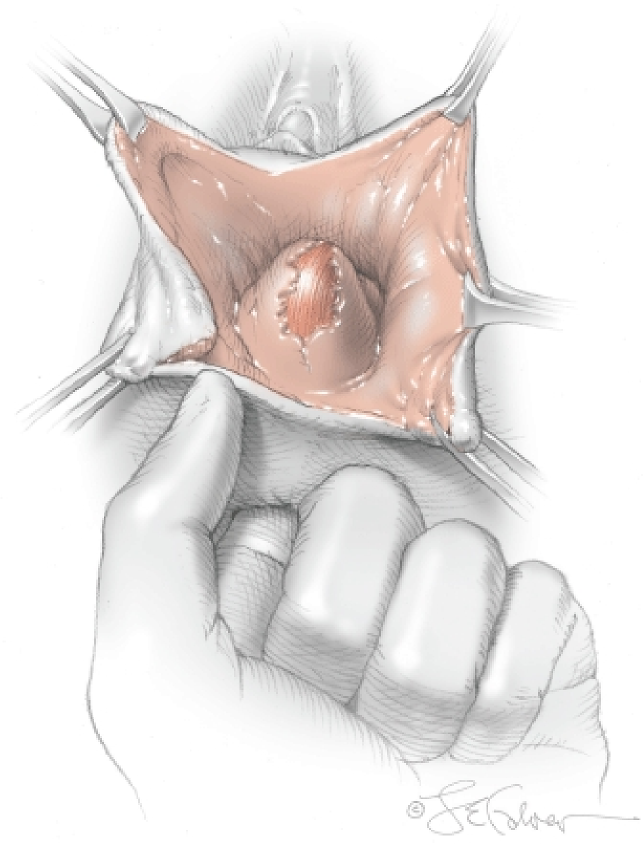


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Vaginal incision and dissection.

3. **Rectal Examination.** Rectal examination is performed to identify the fibromuscular layer as well as the rectal wall and the levator ani muscles (Fig. 42-15.2).

FIGURE 42-15.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

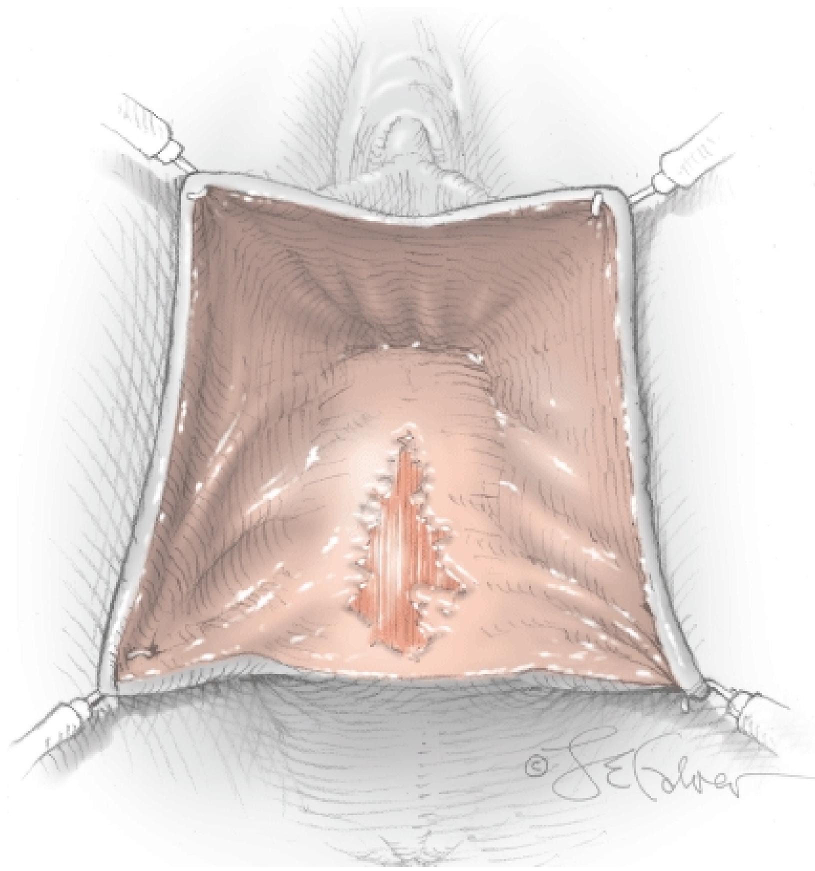
Rectal examination.

4. **Midline Plication.** A series of interrupted 2-0 delayed-absorbable or permanent sutures is used to plicate the vaginal muscularis in the midline, and the line of plication sutures extends from the apex to the perineum (Figs. 42-15.3 and 42-15.4). A second layer of interrupted sutures then plicates muscularis that lies lateral to tissues approximated with the first layer. These sutures are secured in the midline over the first layer.

   Care must be taken to avoid placement of sutures too far laterally because this will lead to a tissue bridge in the posterior vaginal wall with resulting dyspareunia. Additionally, sutures should not be placed in the levator ani muscles because this also may produce dyspareunia and chronic pain. Rectal examination should be performed after all sutures are placed to exclude inadvertent suture placement into the rectum.

   Re-inforcement of the apical aspect of the posterior vaginal wall often is beneficial. If the uterosacral ligaments are identified at the lateral corners of the apex, interrupted sutures are used to connect these ligaments to the upper posterior wall fibromuscular layer.

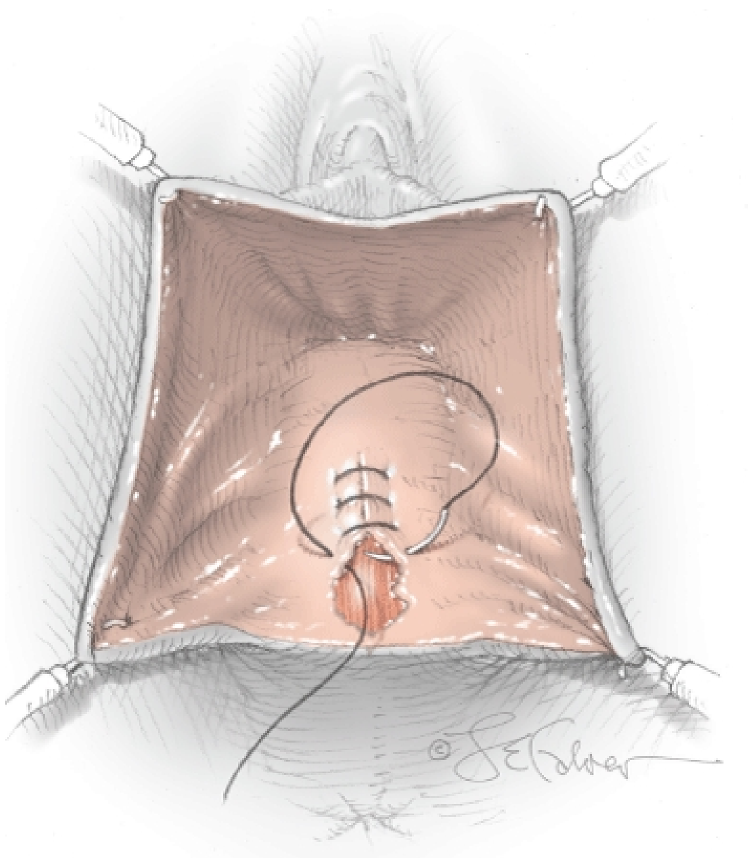
FIGURE 42-15.3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Midline plication.

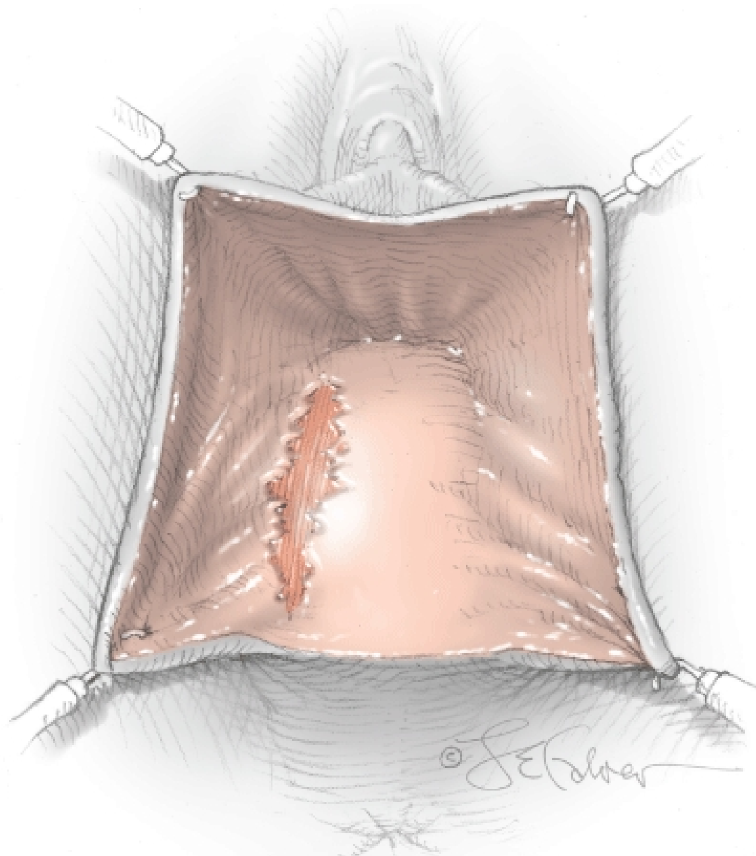
FIGURE 42-15.4



Midline plication.

5. **Defect-Directed Repair.** In some instances, a discrete defect is identified in the posterior fibromuscular layer after the initial dissection. Defects may be lateral, midline, apical, or perineal (Figs. 42-15.5, 42-15.6, 42-15.7, 42-15.8, 42-15.9, and 42-15.10). In this situation, midline plication may not be effective, and a defect repair should be performed. Interrupted stitches of 2-0 permanent or delayed-absorbable sutures are used to close the defect. This is generally a one-layered closure.

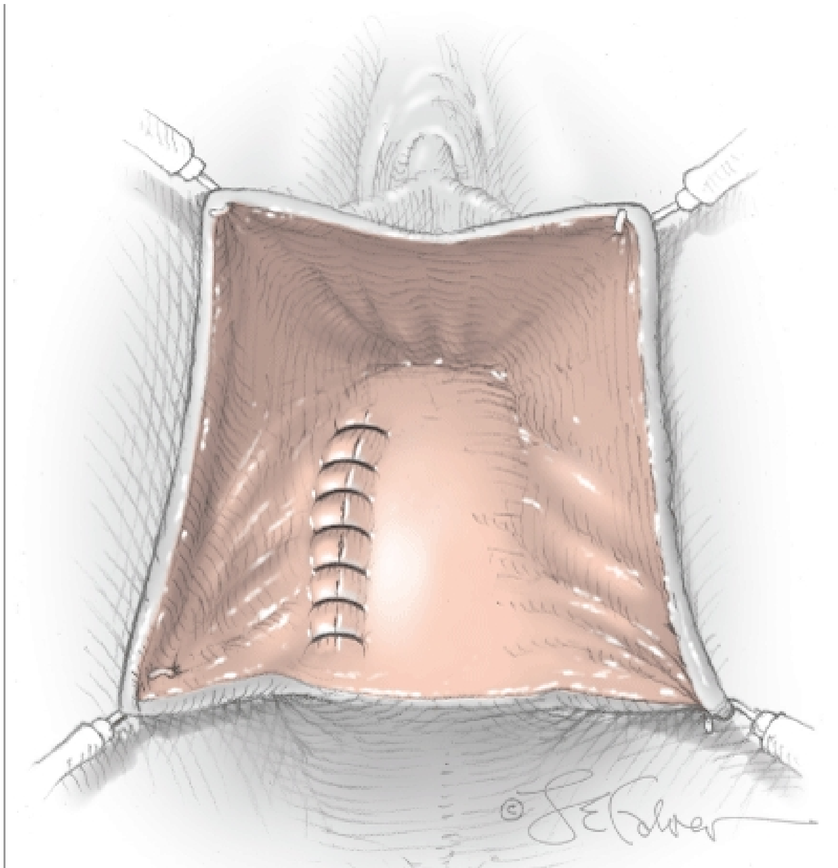
FIGURE 42-15.5



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Defect-directed repair.

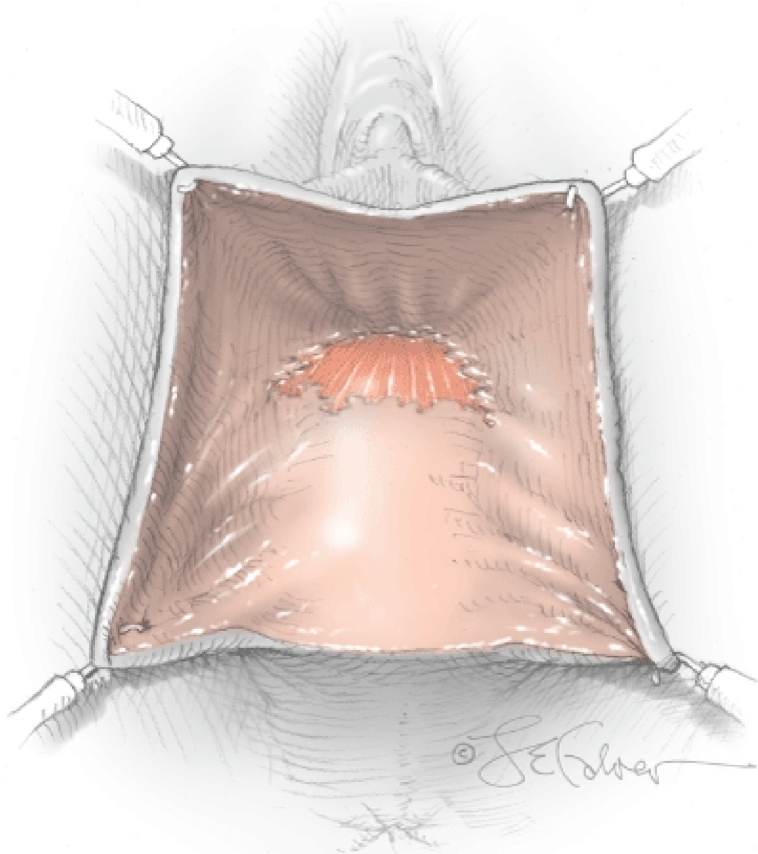
FIGURE 42-15.6



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Defect-directed repair.

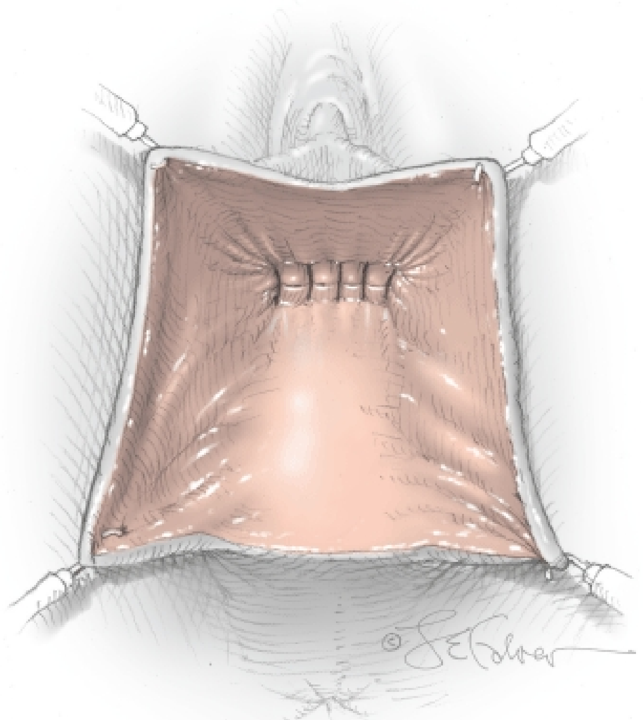
FIGURE 42-15.7



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Defect-directed repair.

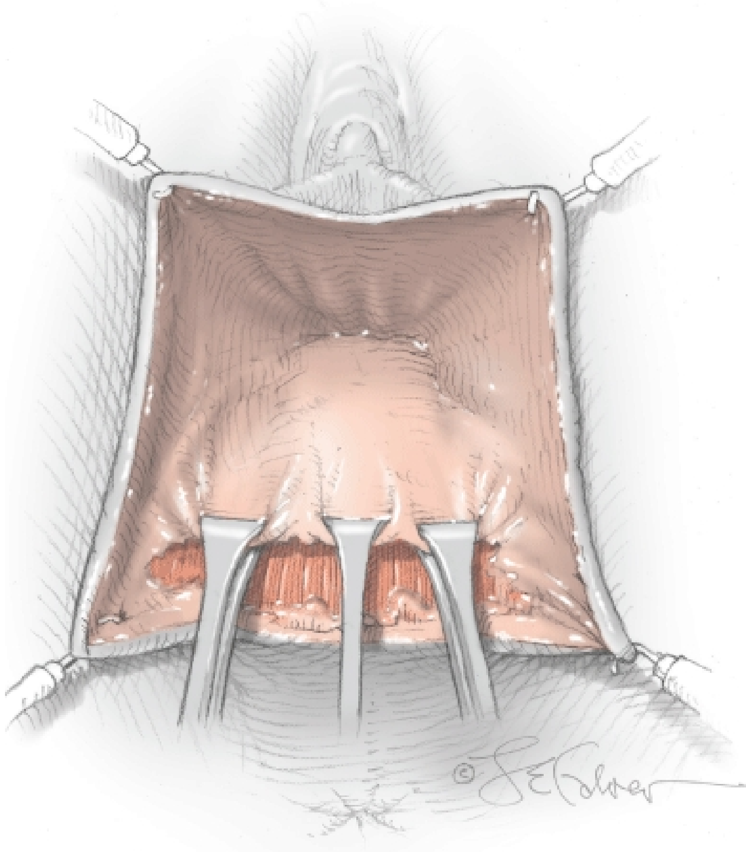
FIGURE 42-15.8



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Defect-directed repair.

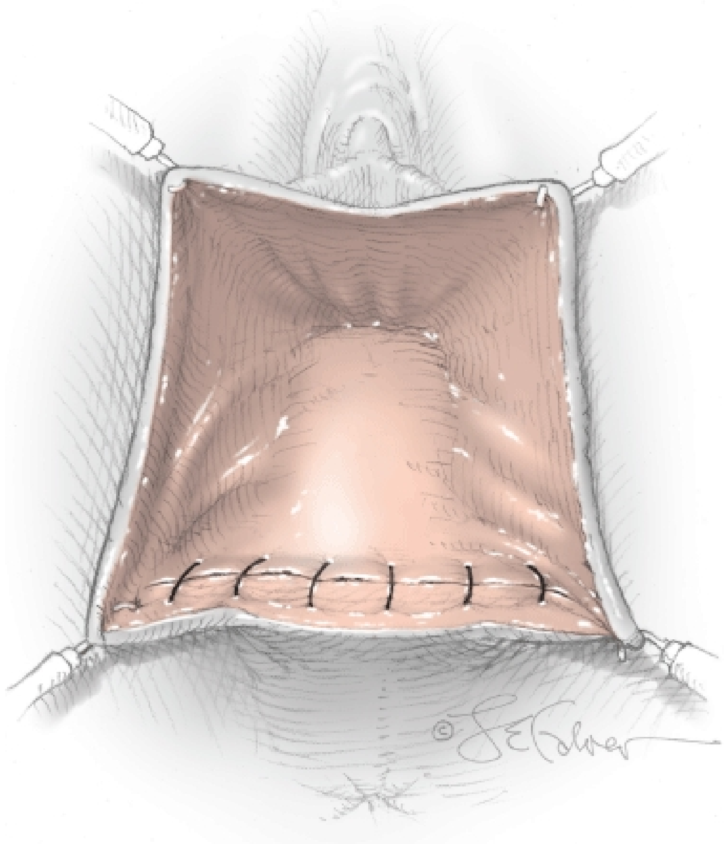
FIGURE 42-15.9



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Defect-directed repair.

FIGURE 42-15.10

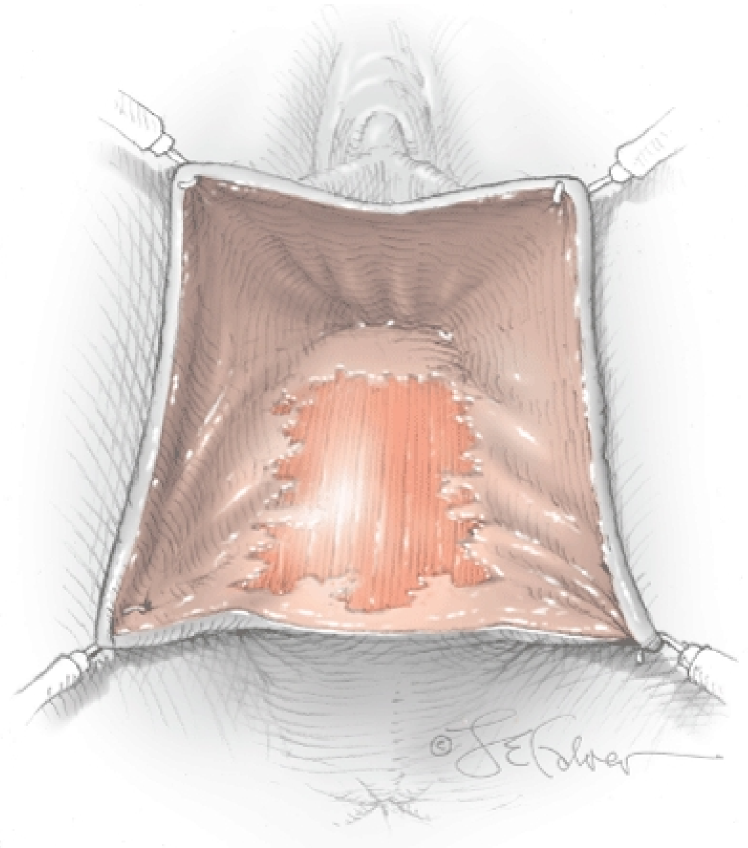


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Defect-directed repair.

6. **Mesh Augmentation.** In situations in which good fibromuscular tissue cannot be identified, synthetic or biologic material can be used for augmentation (Fig. 42-15.11). The initial epithelial dissection is continued laterally and to the apex. The material to be used is cut to size so that it lies flat. It is then sutured with interrupted stitches of 2-0 delayed-absorbable suture to the vaginal apex as well as to the distal and lateral edges of the fibromuscular layer (Fig. 42-15.12). If permanent mesh is used, it should be kept at least 2 cm from the perineal body. The risk of mesh erosion increases as mesh is placed closer to the perineal body. Finally, if the need for mesh augmentation is anticipated, initial dissection is made in a deeper tissue plane to create greater distance between the mesh and vaginal lumen. This hopefully lowers the chance of mesh erosion into the vagina.

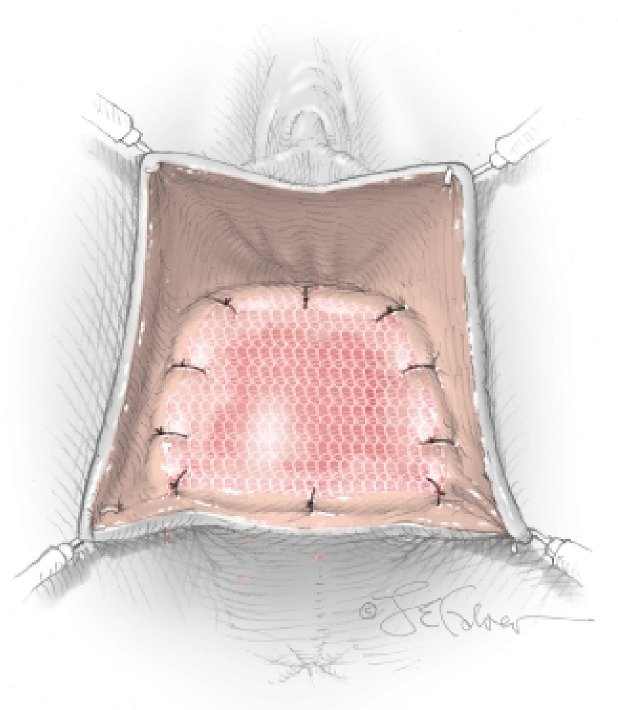
FIGURE 42-15.11



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Mesh augmentation.

FIGURE 42-15.12



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Mesh augmentation.

7. **Perineorrhaphy.** Perineorrhaphy often is performed in conjunction with posterior repair (see Section 42-16, Perineorrhaphy). If performed, it typically follows closure of the vaginal incision.

8. **Incision Closure.** Following plication, redundant vaginal wall often remains and requires trimming. Liberal trimming, however, can narrow the vagina and can place the vaginal wall incision on excessive tension and impair wound healing.

   The vaginal mucosa is reapproximated in a running fashion using a 2-0 delayed-absorbable suture. Care should be taken to avoid placement of suture bites too far apart. Widely positioned sutures can lead to accordion-type bunching of the vaginal epithelium and subsequent shortening of the vagina when the final knot is tied.

Postoperative

Patients are instructed to use twice-daily Sitz bath, stool softeners, and high-fiber diets. Constipation must be meticulously avoided. Intercourse is delayed until evaluation at 1 month postoperatively.

42-16 PERINEORRHAPHY

The perineal body serves as core support of the distal aspect of the vagina, rectum, and pelvic floor. Therefore, a damaged or weakened perineal body may contribute to distal prolapse. Re-inforcement of this structure, that is, perineorrhaphy, often is performed in conjunction with other reconstructive procedures, such as posterior colporrhaphy. As a result of this procedure, a shortened perineal body is lengthened, and the genital hiatus is shortened concurrently to re-establish distal support.

Preoperative

PATIENT EVALUATION

The length of the genital hiatus is measured in centimeters both at rest and with Valsalva maneuver from the urethral meatus at 12 o'clock to the hymeneal ring at 6 o'clock. The perineal body is measured from the hymeneal ring at 6 o'clock to the anus (see Chap. 24, Anterior Vaginal Wall Points). Normative data for these lengths do not exist. Therefore, the decision for perineorrhaphy must include an overall assessment of patient symptoms, clinical findings, and anatomy.

Perineorrhaphy is also sometimes performed for laxity of the introitus with the goal of narrowing the genital hiatus. However, care must be taken not to decrease the caliber to the extent that dyspareunia results. Moreover, in sexually active postmenopausal women whose partners have decreased erectile tone, entry into the vagina may be difficult if the introitus is too small.

CONSENT

A patient preparing for perineorrhaphy should be counseled about risks of postoperative dyspareunia, prolapse recurrence, or wound complications, such as a stitch abscess.

PATIENT PREPARATION

Because of the surgical site's close proximity to the anus, and also because bowel injury is possible, bowel preparation and antibiotic prophylaxis are administered prior to surgery. These are given to minimize the risks of fecal contamination and wound infection.

Intraoperative

Surgical Steps

1. **Anesthesia and Patient Positioning.** Perineorrhaphy typically is performed under general or regional anesthesia, and this choice is often dictated by concurrent surgeries planned. The patient is placed in dorsal lithotomy position. A vaginal and rectal examination under anesthesia is performed first to assess the size of the perineal body and defects of the posterior vaginal wall, which also may require repair. The vagina is surgically prepared, and a Foley catheter is placed.

2. **Concurrent Surgery.** If concurrent surgeries have been included, perineorrhaphy in most cases is the final procedure.

3. **Incision.** To determine the approximate appearance of the final repair, Allis clamps are placed at the corners of the introitus at 3 and 9 o'clock. These are brought together in the midline. With this technique, the surgeon can judge the final size of the introitus and perineal body anticipated at the procedure's conclusion. Because scarring and retraction can follow surgery, it is prudent to err on the side of leaving the genital hiatus larger rather than smaller. Although each case is individualized, in general, the introitus should admit three fingers at the end of surgery.

   A diamond-shape incision is made with its cephalad tip extending 2 to 3 cm into the vagina and the caudal tip extending to a point approximately 2 cm above the anus.

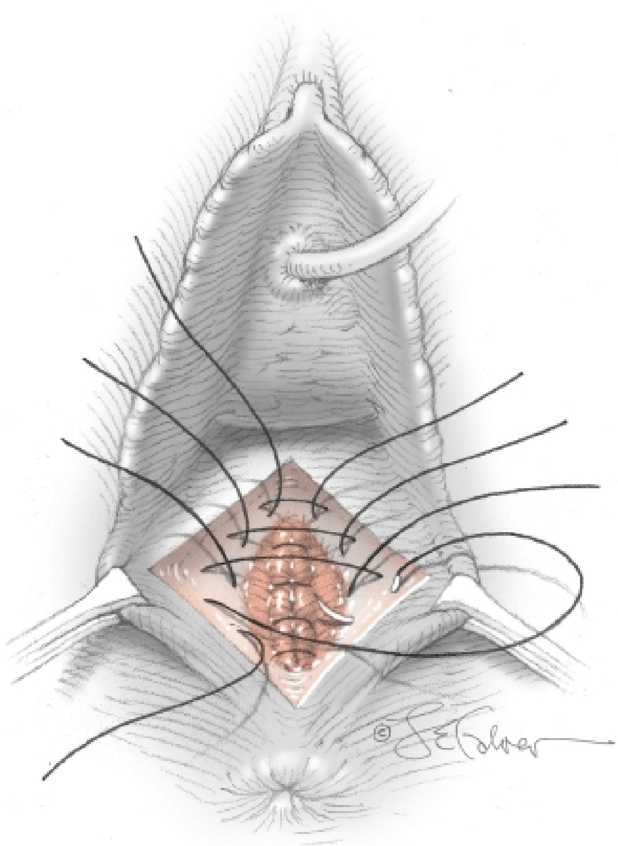
4. **Removal of Skin and Mucosa.** For traction, an Allis clamp is placed at the lowermost tip of the diamond. Metzenbaum scissors are use to excise the perineal skin and vaginal mucosa within the diamond from the underlying tissue. During dissection, the scissor tips are held parallel to the vaginal tissue.

   Sharp dissection must be performed over the perineal body. This area contains a normal condensation of tissue, and additionally, scarring may be present. As a result, development of good tissue planes may not always be possible. Accordingly, frequent rectal examination during dissection may be required to prevent entry into the rectum.

5. **Suture Placement.** One centimeter distal to the hymeneal ring, a 0-gauge delayed-absorbable suture on a CT-1 needle is used to approximate the perineal muscles. In suturing these muscles, a wide lateral bite is taken, and suture is directed first in an inward-to-outward and then outward-to-inward sequence (Fig. 42-16.1). This suture technique effectively buries knots below the plicated muscles. However, initially, the first suture is held and not tied.

   Downward traction is placed, and a second suture is positioned approximately 1 cm cephalad. A third suture can be placed 1 cm further cephalad to this, if necessary. In a similar fashion, one to two stitches are placed 1 cm apart and caudal to the primary suture. The sutures then are tied progressively beginning with the lowermost. In some cases, a second running layer is placed in the superficial perineal muscles for additional support.

FIGURE 42-16.1



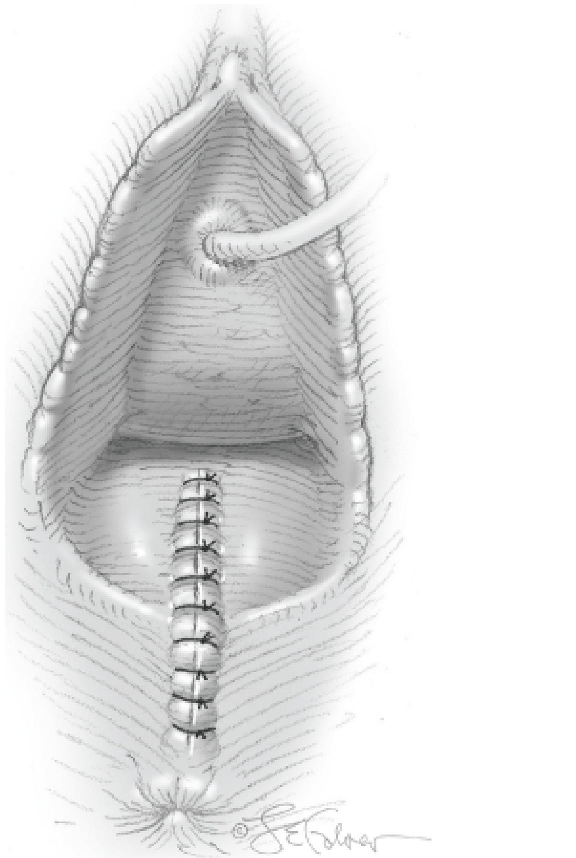
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Suture placement.

6. **Vaginal and Perineal Closure.** Starting at the vaginal apex, the vaginal mucosa is closed in a running fashion using 2-0 delayed-absorbable suture (Fig. 42-16.2). The surgeon should be mindful that sutures, when creating a running suture line in the vagina, should be placed close together. If suture bites are placed far apart during mucosal closure, the vagina can be shortened.

   The running suture re-approximates the hymeneal ring and then is brought into the perineal area. The same suture then is used in a running mattress method to reapproximate the subcutaneous tissue to the end of the incision, near the anus. Interrupted stitches of of 3-0 delayed-absorbable suture are used to close the perineal skin.

FIGURE 42-16.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Wound closure.

Postoperative

Patients are instructed to used twice-daily sitz baths, stool softeners, and high-fiber diets. Constipation must be meticulously avoided. Intercourse is delayed until evaluation at 1 month postoperatively. We have found that perineorrhaphy and posterior repair may be associated with short-term urinary retention. This is believed to result from spasm of the levator ani muscles. Therefore, a voiding trial is recommended postoperatively, with assessment of postvoid residuals (see Chap. 39, Voiding Trials).

42-17 ABDOMINAL SACROCOLPOPEXY

Since its introduction in the early 1960s, abdominal sacrocolpopexy has become a widely accepted transabdominal procedure that suspends the vaginal vault to the sacrum using natural or synthetic grafts (Lane, 1962). This procedure is performed primarily to resuspend a prolapsed vaginal apex. Secondary indications include repair of apical segment descent of the anterior vaginal wall (cystocele) and posterior vaginal wall apical segment descent (enterocele and rectocele). A modification of the procedure, *sacrocolpoperineopexy,* is used to repair perineal descent (Weidner, 1997).

Sacrocolpopexy is one of several primary operations chosen for vaginal apex resuspension because of its ability to maintain normal vaginal anatomy and its durability. Long-term success rates range near 90 percent. It may be used as a primary procedure or alternatively, as a second surgery for patients with recurrences after failure of other prolapse repairs. In addition, it is ideal for those believed to be at high risk for recurrence, for example, those with chronically increased intra-abdominal pressure. Such

candidates may include those with chronic obstructive pulmonary disease or chronic constipation, connective tissue disease, history of recurrent hernia, or obesity. In these women, mesh provides augmentation to the patient's own tissues.

Although the vaginal apex also can be suspended successfully with vaginal approach procedures such as sacrospinous ligament fixation (see Section 42-20, Sacrospinous Ligament Fixation) and uterosacral ligament suspension (see Section 42-19, Vaginal Uterosacral Ligament Suspension), sacrocolpopexy offers distinct advantages. Sacrocolpopexy maintains or lengthens the vagina, in contrast to vaginal approaches, which tend to shorten it. Second, the use of permanent mesh with multiple attachment sites to the vagina has a very low risk of failure. Finally, unlike vaginal approaches, the vaginal apex typically remains mobile, thus possibly lowering the risk for dyspareunia.

Sacrocolpopexy provides durable support over time by attaching the vaginal apex and the anterior and posterior vaginal walls to the anterior longitudinal ligament of the spine at the level of the sacrum. Although grafts of autologous, cadaveric, or synthetic materials may be used, permanent (synthetic) mesh has the best success rate and should be used unless otherwise contraindicated (Culligan, 2005).

Sacrocolpopexy also is performed laparoscopically by skilled laparoscopic surgeons. If the laparoscopic operation is performed in the same manner as the open operation, similar results can be expected.

Preoperative

PATIENT EVALUATION

Prior to sacrocolpopexy, patients with symptoms of urinary incontinence should undergo simple or complex urodynamic testing to determine the need for an anti-incontinence procedure (see Chap. 23, Diagnostic Testing). Similarly, women without incontinence also should undergo testing with reduction of the prolapse to assess whether repair will unmask incontinence.

Prolapse of the vaginal apex often coexists with other sites of prolapse along the vaginal vault. For this reason, a careful preoperative assessment should be performed and concurrent prolapse of the anterior or posterior vaginal walls identified, as described in Chapter 24, Perineal Examination. If necessary, sacrocolpopexy can be performed concurrently with paravaginal defect repair, posterior colporrhaphy, or other prolapse procedures. In addition, a modification of the procedure known as sacrocolpoperineopexy may be performed to correct perineal descent. Beer and Kuhn (2005) found that approximately 70 percent of abdominal sacrocolpopexy procedures were performed with other pelvic reconstructive operations.

With the technique we describe, a concurrent enterocele will be repaired by the colpopexy. For this reason Halban- or Moschcowitz-type enterocele repairs are unnecessary. These two repairs close the cul-de-sac of Douglas but have not been proven to decrease prolapse recurrence and may worsen defecatory dysfunction.

In patients with real or potential stress urinary incontinence, a concurrent anti-incontinence operation is performed. The CARE (Colpopexy After Reduction Efforts) trial found that patients without urinary incontinence symptoms undergoing sacrocolpopexy for prolapse of the anterior vaginal wall to within 1 cm of the hymen developed bothersome urinary incontinence in 24 percent of cases. Only 6 percent of those that had a concurrent Burch procedure developed bothersome incontinence (Brubaker, 2006).

CONSENT

As with any prolapse repair, the most important long-term risk is recurrent prolapse. The individual surgeon should be aware of the recurrence rates quoted in the literature of 10 to 15 percent, as well as his or her own personal recurrence rates. Although vaginal apex prolapse recurrence is infrequent, prolapse of the anterior and posterior vaginal walls is common.

Mesh erosion is another complication, developing in 2 to 5 percent of patients. This may develop soon after surgery or years later. Mesh erosion generally is found at the apex and is more common if sacrocolpopexy is performed concurrently with hysterectomy.

PATIENT PREPARATION

Bowel Preparation

Because of the risk of bowel injury during dissection of the sigmoid colon and rectum, a cleansing evacuation is recommended the evening prior to surgery (see Table 39-10).

Antibiotic Prophylaxis

Although this practice has not been rigorously investigated in randomized trials, antibiotics are given preoperatively to decrease the risk of graft infection as well as other abdominal infections.

Medications

Vaginal estrogen cream use during the 6 to 8 weeks prior to surgery has been recommended routinely. It is believed that estrogen treatment enhances vascularity to promote healing and increase tissue strength. Although this is common practice and seems logical, there are no data to suggest that preoperative vaginal estrogen cream is beneficial.

Intraoperative

INSTRUMENTS AND MATERIALS

The upper vagina and vaginal apex must be elevated and distended with a vaginal stent to allow adequate dissection and delineation of the vaginal wall's fibromuscular layers and mesh placement. The vaginal stent may be a large EEA (end-to-end anastomosis) sizer (see Fig. 42-17.5), which is present in most operating rooms, or a cylindrical lucite rod.

The ideal bridging material for this procedure is permanent, nonantigenic, easily cut and customized, and readily available. Although autologous and cadaveric materials have been used, they are not as effective as synthetic mesh, and their use is discouraged. The ideal mesh has a large pore size to allow host tissue ingrowth, is monofilament to decrease bacterial adherence, and is easily manipulated (see Fig. 24-21).

SURGICAL COMPLICATIONS

Significant hemorrhage can develop during dissection and suture placement at the anterior longitudinal ligament. A thorough knowledge of pelvic anatomy is essential to prevent and manage such hemorrhage. The most common vessels lacerated during sacrocolpopexy are the presacral venous plexus and the middle sacral vessels (see Fig. 38-24). Suturing at S3 or S4 vertebral bodies increases the risk of injury to the presacral venous plexus. In contrast, placement of sutures at S1 or the sacral promontory risks laceration of the middle sacral vessels or the left common iliac vein (Wieslander, 2006). At S1, however the middle sacral vessels are readily visible and can be isolated and avoided easily. Additionally, at S1, the anterior longitudinal ligament is thicker and stronger. Affixing sutures into this thicker portion of the ligament minimizes the risk of suture avulsion. For these reasons, many surgeons currently choose to place sutures at S1 or at the level of the sacral promontory (Nygaard, 2004).

With hemorrhage from these vessels, several steps may be critical to its control. First, pressure is applied immediately and held for several minutes. This may be particularly effective for venous bleeding. Sutures and clips may be useful, but injury of small veins frequently worsens with suturing. Additionally, as vessels retract into the bone, isolation and ligation become difficult. Sterile thumbtacks directed through the lacerated vessels and pushed into the sacrum can effectively compress such vessels. Unfortunately, these tacks are not found routinely in many operating rooms.

Alternatively, various local hemostatic agents have been used to control bleeding refractory to these initial steps (see Table 40-5). Although no studies have compared these agents in urogynecologic procedures, animal and vascular studies have shown FloSeal Matrix (Fusion Medical Technologies, Mountain View, CA) to be very effective (Kheirabadi, 2002; Oz, 2000; Weaver, 2002). Moreover, the granular nature of FloSeal Matrix allows conformation to irregular wounds, which is a distinct advantage in managing hemorrhage typical of sacrocolpopexy.

Surgical Steps

1. **Anesthesia and Patient Positioning.** Following administration of general anesthesia, the patient is positioned supine in Allen stirrups. Correct positioning, as described in Chapter 40, Patient Positioning, with no pressure on the calf or thigh and with the thigh parallel to the ground, will decrease the risk of nerve injury. Moreover, this positioning allows excellent access to the vagina and proper placement of the abdominal self-retaining retractor. The buttocks are positioned at the edge of the table or slightly distal to allow full range of vaginal stent manipulation. The vagina and abdomen are surgically prepared, and a Foley catheter is placed.

2. **Incision.** A vertical or transverse abdominal incision as described in Sections 41-1, Midline Vertical Incision and 41-2, Pfannenstiel Incision may be used. Incision selection is directed by a woman's body habitus and by planned concurrent procedures. A Pfannenstiel incision generally provides adequate access to the sacrum and deep pelvis.

   Prior to skin incision, the sacral promontory should be palpated through the abdominal wall deep to the umbilicus. The incision then is placed at a level that allows access to both vaginal apex and promontory. If a Burch colposuspension, paravaginal defect repair, or other surgery in the space of Retzius is planned, then a Pfannenstiel incision that is positioned closer to the symphysis is preferred.

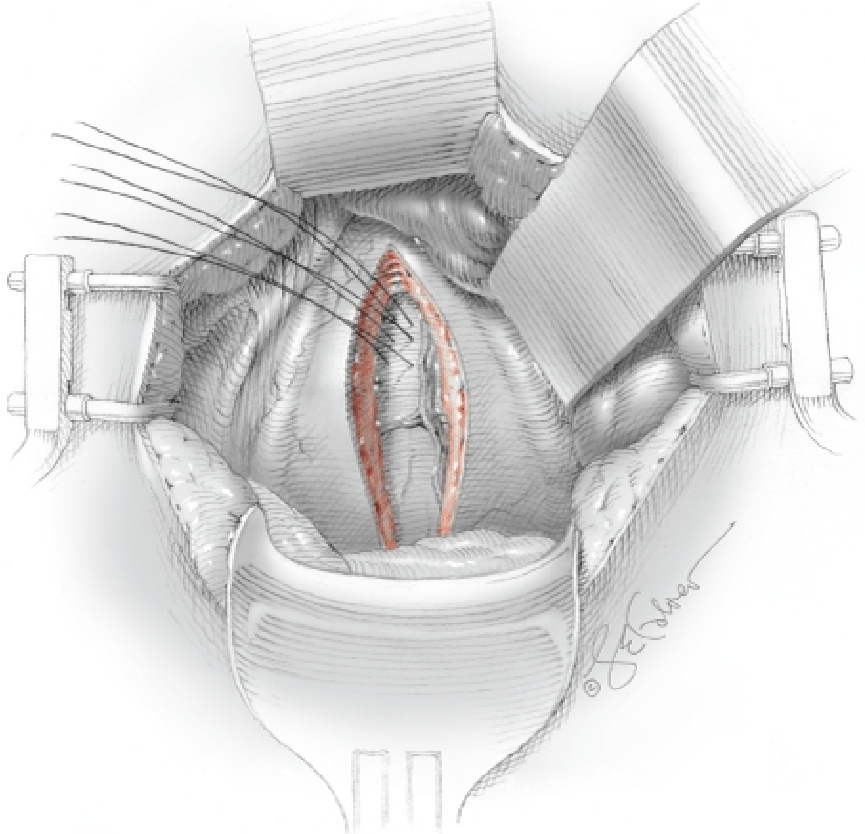
3. **Bowel Packing.** A self-retaining retractor, preferably a Balfour or Bookwalter type, is placed, and the bowel is packed up and out of the pelvis with laparotomy sponges. Bowel packing should attempt to shift the sigmoid colon to the patient's left, thereby allowing access to the sacrum.

4. **Identification of Anatomic Structures.** The aortic bifurcation and iliac vessels are identified, and the middle sacral vessels are palpated ventral to the sacral promontory in the midline. In addition, tracing the course of both ureters aids in avoiding their injury. Specifically, the right ureter is at greater risk than the left during suture placement at the sacrum.

5. **Peritoneal Incision.** The peritoneum overlying the sacral promontory in the midline is elevated with forceps and incised sharply. The incision is extended caudally into the cul-de-sac of Douglas. Closure of this incision at the end of surgery allows the mesh to lie beneath the peritoneum. This may decrease the risk of future adhesion of bowel to mesh.

6. **Placement of Sacral Sutures.** A Kitner sponge is used to gently dissect and remove fat and areolar tissue from the sacrum. Beneath these tissues, the shiny white anterior longitudinal ligament is seen to overlie the bone in the midline. As stated previously, sutures may be placed at S1 through S4. Three sutures of 2-0 permanent material, each double-armed with SH needles, are used. The needle is driven either horizontally or vertically through the anterior longitudinal ligament. Suture placement is determined by each patient's anatomy and ease of placement (Fig. 42-17.1). There is no evidence to suggest that horizontal placement is superior to vertical placement, or vice versa. In some situations, damage to the middle sacral vessels may be avoided by horizontal placement of the sutures around the vessels. Ideally, each suture lies about Â½ cm apart. These sutures, with needles attached, then are held by a hemostat until later in the case.

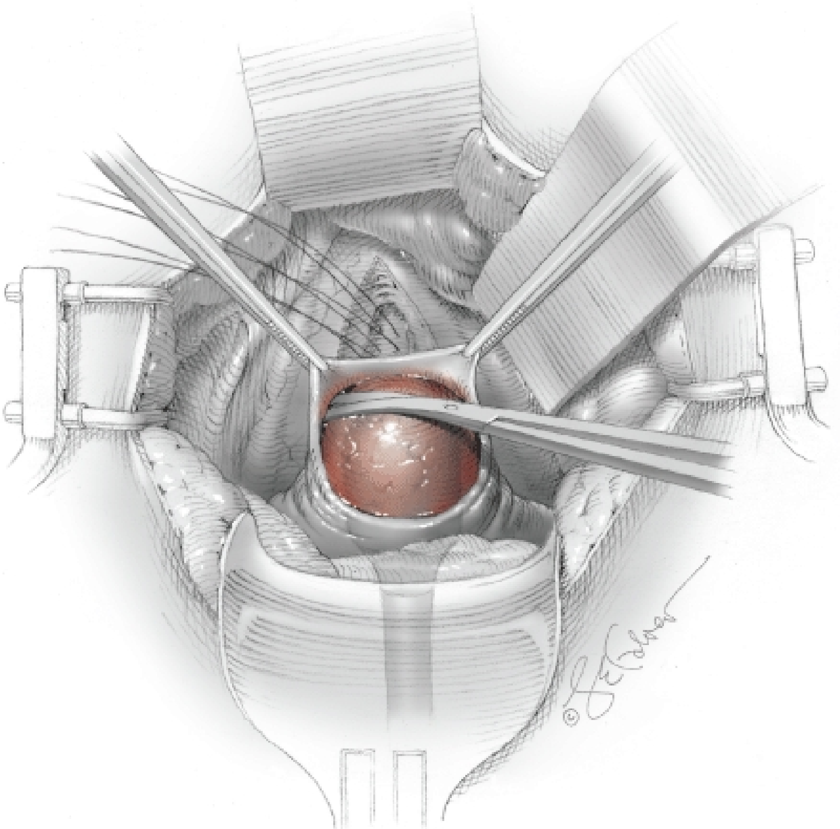
FIGURE 42-17.1



Placement of sacral sutures.

7. **Dissection of the Anterior Vaginal Wall.** A vaginal stent is placed to elevate the vaginal apex, and the peritoneum covering the apex is incised transversely. Sharp and blunt dissection is used to separate the peritoneum and bladder from the anterior vaginal wall (Fig. 42-17.2). This anterior dissection extends approximately 5 to 6 cm caudally to create an extensive surface for mesh fixation. Dissection should progress at a depth above the fibromuscular layer of the vaginal wall. Entry into the proper plane above the fibromuscular layer will decrease the risk of incidental entry into the vagina. Accidental opening of the vaginal wall increases the risk of future mesh erosion secondary to bacterial exposure. If the vaginal wall is opened, it should be irrigated copiously followed by a two-layered imbricating closure with 2-0 or 3-0 delayed-absorbable suture.

FIGURE 42-17.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

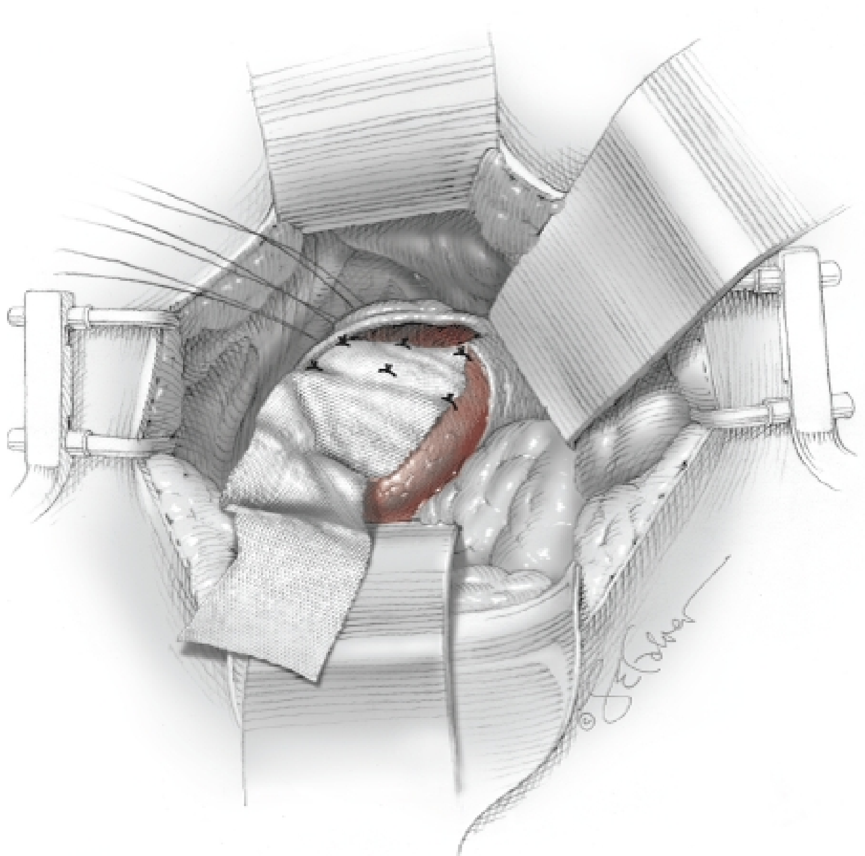
Dissection of the anterior vaginal wall.

8. **Dissection of the Posterior Vaginal Wall.** The vaginal apex is grasped with Allis clamps, pressure is released on the EEA sizer, and the peritoneum covering the posterior vaginal wall then is opened. The rectovaginal space is identified and entered. Blunt dissection further opens this space to the level of the rectal reflection. If sacrocolpoperineopexy is planned, dissection continues beyond the rectal reflection to the level of the perineal body.

   Two rectangular pieces of mesh then are cut to the width of the dissected anterior and posterior vaginal wall surfaces. They are left long to allow fixation to the sacrum later in the procedure.

9. **Posterior Mesh Placement.** For mesh attachment, 2-0 permanent suture is recommended. Six sutures are used at the edges of the mesh to secure it to the vaginal wall's fibromuscular layer. We prefer two rows of three sutures (Fig. 42-17.3). The bottom row is placed at the distal edge of the mesh. Care is taken to avoid placing sutures at the vaginal apex because this is the least vascular region and therefore susceptible to suture and mesh erosion. Attempts are made to avoid penetration of the vaginal epithelium with these sutures. However, if the fibromuscular layer is thin, this will not be possible, and the epithelium is incorporated. These vaginal sutures generally will be epithelialized postoperatively.

FIGURE 42-17.3

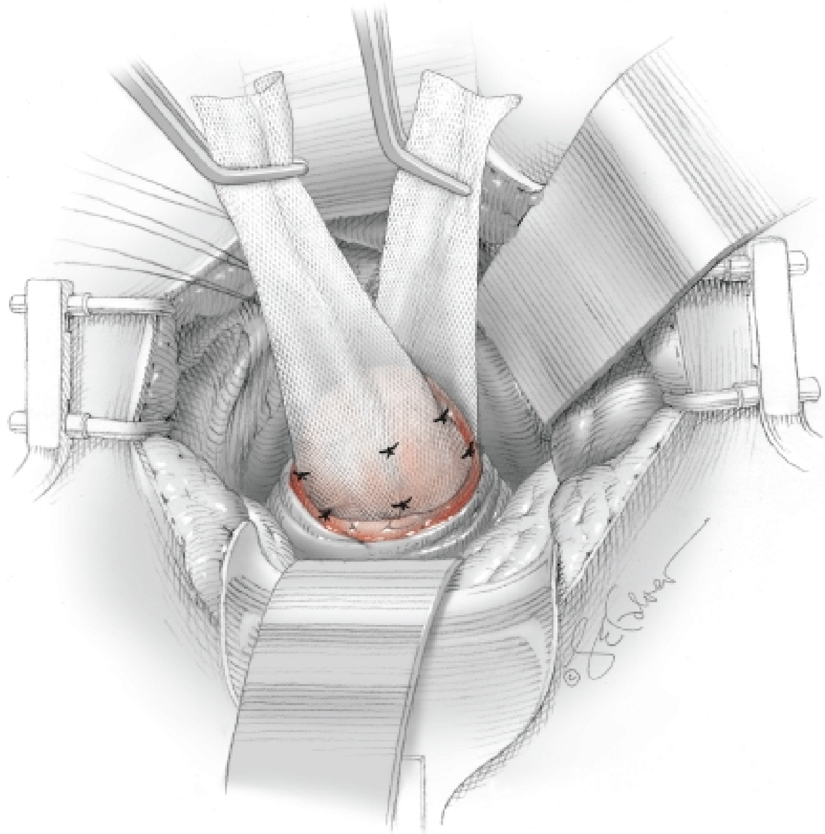


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Posterior mesh placement.

10. **Anterior Mesh Placement.** With the vaginal stent serving as a support, mesh is sutured to the anterior vaginal wall in exactly the same fashion as was performed on the posterior vaginal wall (Fig. 42-17.4). In general, the length of the mesh used on the anterior vaginal wall is shorter than that on the posterior vaginal wall.

FIGURE 42-17.4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

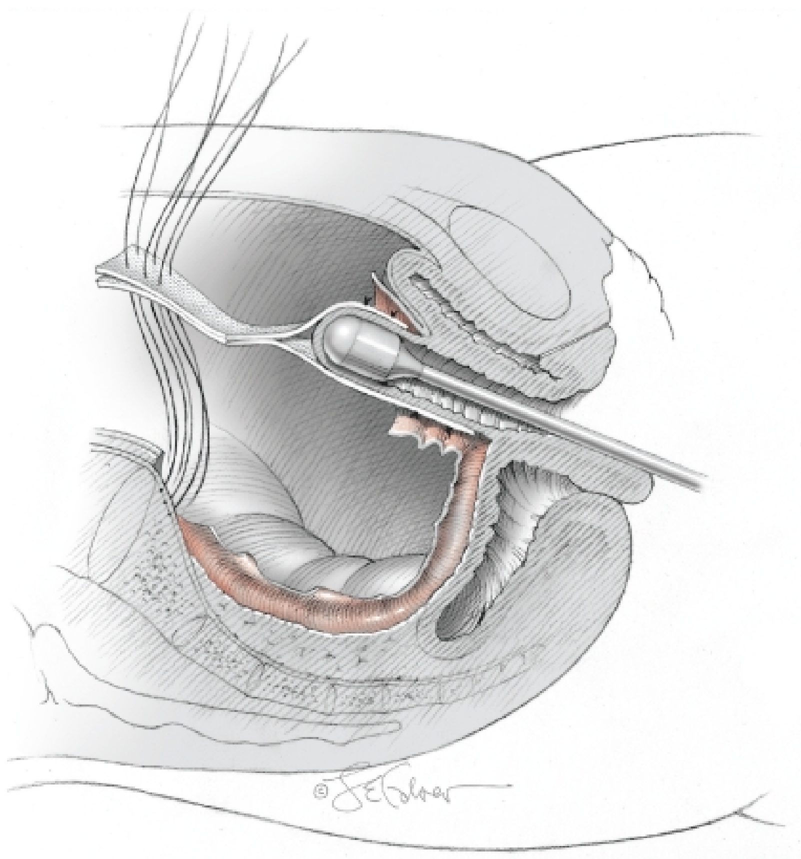
Anterior and posterior mesh in place.

11. **Passage of Mesh into Peritoneal Tunnel.** After the anterior and posterior meshes are secured, both are passed through the peritoneal tunnel to the sacral sutures.

12. **Vaginal Peritoneal Closure.** The peritoneum is closed over the vaginal apex with 2-0 delayed-absorbable suture in a running fashion.

13. **Mesh Sizing and Attachment to the Sacrum.** The vaginal stent is removed, and digital examination of the vagina is performed. The length of mesh necessary for adequate support is estimated by holding the mesh to the sacrum with the abdominal hand and palpating vaginally. Apical suspension should reduce prolapse of the apex as well as the apical segments of the anterior and posterior vaginal walls. If possible, the mesh should not be placed on tension and then is cut to the appropriate length. The six needles of the three double-armed sacral sutures then are passed through the proximal end of the mesh (Fig. 42-17.5). Each of the three paired sutures then is knotted to secure the mesh to the anterior longitudinal ligament (Fig. 42-17.6).

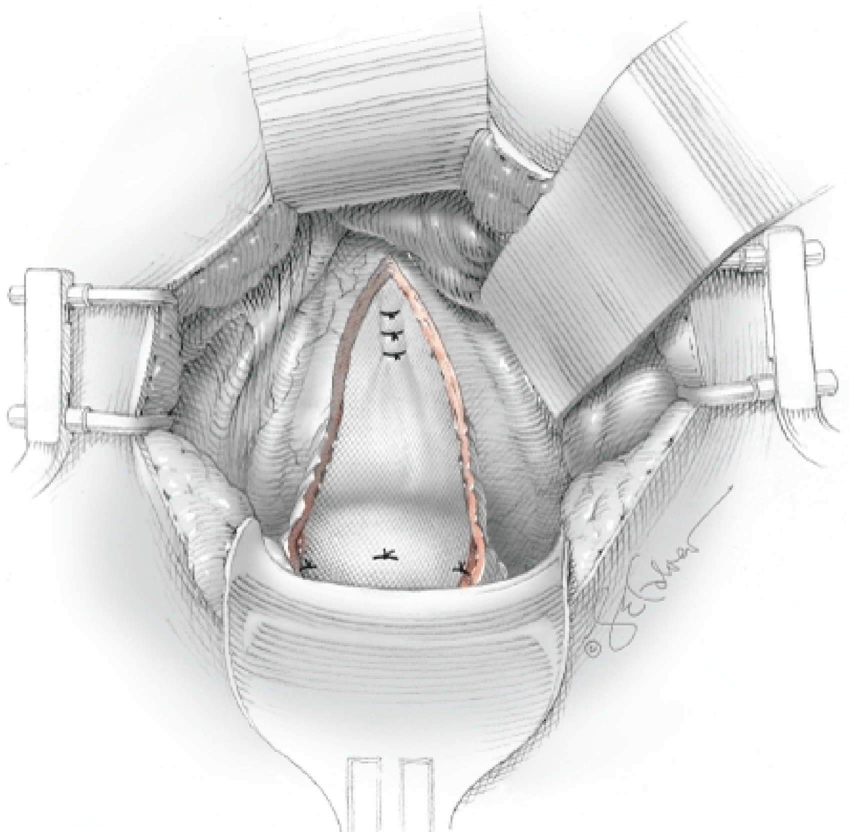
FIGURE 42-17.5



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Mesh attachment to the sacrum.

FIGURE 42-17.6

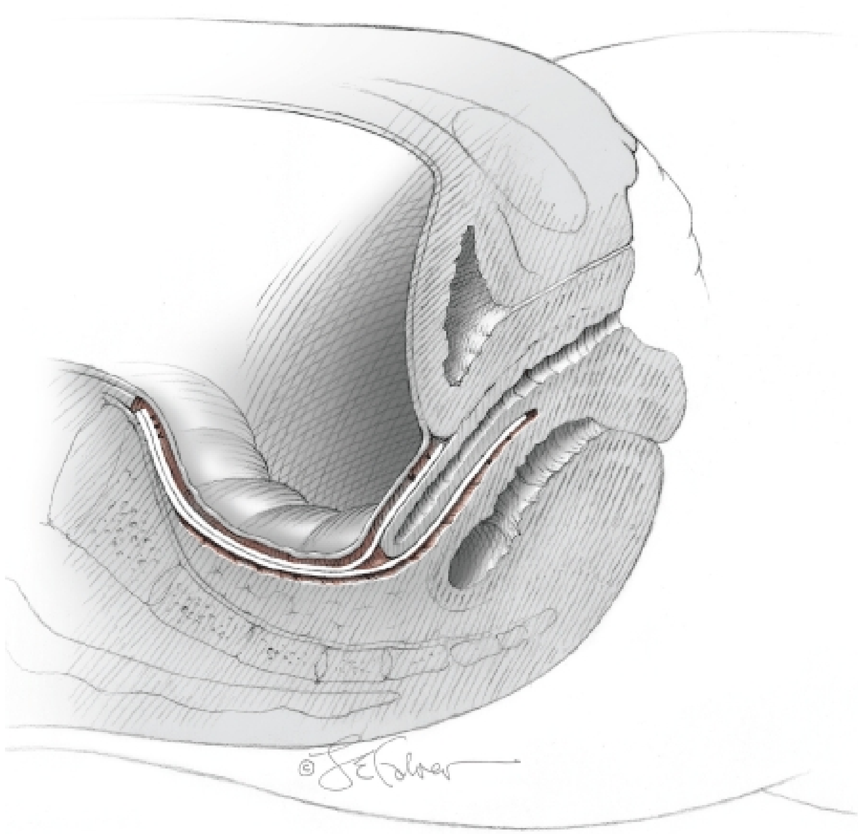


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Final mesh placement.

14. **Peritoneal Closure.** The peritoneum is closed over the mesh to the level of the sacral promontory, completely burying the mesh retroperitoneally (Fig. 42-17.7).

FIGURE 42-17.7



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Peritoneal closure.

15. **Cystoscopy.** Cystoscopy is performed to ensure ureteral integrity (see Section 42-1, Diagnostic and Operative Cystoscopy and Urethroscopy).

16. **Abdominal Closure.** The abdomen is closed in a standard fashion (see Sections 41-1, Midline Vertical Incision or 41-2, Pfannenstiel Incision).

Postoperative

COMPLICATIONS

Following sacrocolpopexy, the graft material or its attaching sutures can erode through the vaginal muscularis and then the mucosa. This is a frequently cited complication of the procedure but fortunately is uncommon and develops in 2 to 5 percent of cases (Beer, 2005; Nygaard, 2004). Symptoms develop, on average, 14 months following surgery and classically consist of vaginal bleeding and discharge (Kohli, 1998). The diagnosis is straightforward because mesh or sutures can be seen directly on speculum examination.

Of note, recurrent bouts of granulation tissue without visible erosion most likely represent an invisible mesh or suture erosion.

Mesh erosion through the vaginal mucosa may be treated initially with a 6-week course of intravaginal estrogen vaginal cream. For

those in whom epithelium fails to cover the mesh, surgical removal is performed vaginally. The mesh is grasped, placed on tension, and as much mesh as can be identified is resected. The mucosal edges bordering the erosion site are dissected away from the mesh, undermined, and re-approximated. Failure of these wounds to heal should be interpreted as a sign of graft infection, and the graft material should be removed completely either vaginally or abdominally (Mattox, 2004). Similarly, suture erosion of sutures may be managed by removal in the office.

Fortunately, removal of sutures and eroding mesh does not compromise the prolapse repair. In most cases postoperative scarring continues to hold the vaginal apex suspended.

PATIENT CARE

Postoperative in-hospital management is similar to that for other intra-abdominal surgeries. Foley catheter management depends on whether an anti-incontinence procedure was performed. In the absence of such procedures, the catheter can be removed routinely on the first postoperative day. A stool softener should be prescribed as soon as a regular diet is tolerated, and care should be taken to avoid constipation after discharge from the hospital.

At routine postoperative visits, evaluation for prolapse recurrence and mesh or suture erosion should be performed. Symptoms of pelvic floor dysfunction also should be elicited at all postoperative visits. Anatomic success does not always correlate with functional success, and vice versa. Therefore, it is important to continually evaluate the results of surgery based on anatomy as well as symptoms such as urinary incontinence, defecatory dysfunction, pelvic pain, and sexual dysfunction.

42-18 ABDOMINAL UTEROSACRAL LIGAMENT SUSPENSION

Suspension of the vaginal apex can be performed effectively with a variety of vaginal or abdominal surgeries, and success rates approximate 90 percent. Selection of procedure approach is based on a comprehensive assessment of a woman's symptoms and anatomy, as well as surgeon preference. For patients undergoing abdominal surgery, there are two choicesâ€”uterosacral ligament suspension (USLS) and abdominal sacrocolpopexy. Of these two, USLS may be performed in patients with well-defined uterosacral ligaments. In addition, USLS is often preferred for those undergoing hysterectomy because abdominal sacrocolpopexy carries an increased risk of mesh erosion if performed concurrently with hysterectomy (see Sections 42-17, Abdominal Sacrocolpopexy).

During USLS, the uterosacral ligaments are sutured to the anterior and posterior vaginal walls at the vaginal apex. With this suspension, enteroceles are effectively closed. Thus, adjunctive Halban or Moschowitz culdoplasty enterocele repairs are not required.

Preoperative

PATIENT EVALUATION

Prior to USLS, patients with symptoms of urinary incontinence should undergo simple or complex urodynamic testing to determine the need for an anti-incontinence procedure (see Chap. 23, Diagnostic Testing). Patients without incontinence also should undergo testing with reduction of their prolapse to assess whether repair will unmask incontinence.

Prolapse of the vaginal apex often coexists with other sites of prolapse along the vaginal vault. For this reason, a careful preoperative assessment should be performed and concurrent prolapse of the anterior or posterior vaginal walls identified, as described in Chapter 24, Perineal Examination. If necessary, USLS can be performed with paravaginal defect repair, posterior colporrhaphy or other prolapse procedures. In patients with real or potential stress urinary incontinence, a concurrent anti-incontinence operation is performed.

CONSENT

The consent process for USLS should include discussion of general risks associated with abdominal surgery, as well as specific risks associated with the procedure. As with any prolapse repair, the most important long-term risk is recurrence. Thus, surgeons should be aware of recurrence rates quoted in the literature of 10 to 15 percent, as well as their own personal recurrence rates. Although recurrence of vaginal apex prolapse is infrequent, later prolapse of the anterior and posterior vaginal walls is common.

Urinary incontinence also may develop after USLS if an anti-incontinence procedure is not performed. Therefore, preoperative

discussion of bladder function after surgery is essential. Uterosacral ligament suspension does have a potential to shorten and fix the upper vagina. As a result, dyspareunia is a postoperative risk and should be discussed. Additionally, nerve injury with subsequent neuropathy has been reported.

PATIENT PREPARATION

During USLS, an end-to-end anastomoses (EEA) sizer may be placed for rectosigmoid colon manipulation (see Fig. 42-17.5). For this reason, and because of the small but potential risk of bowel injury, bowel preparation is recommended (see Table 39-10). Additionally, antibiotic prophylaxis is provided prior to surgery (see Table 39-7).

Intraoperative

Surgical Steps

1. **Anesthesia and Patient Positioning.** This inpatient procedure is performed under general or regional anesthesia. The patient's legs are placed into Allen stirrups and positioned in a low lithotomy position with the thighs parallel to the ground (see Fig. 40-6).The vagina and abdomen are surgically prepared, and Foley catheter is placed.

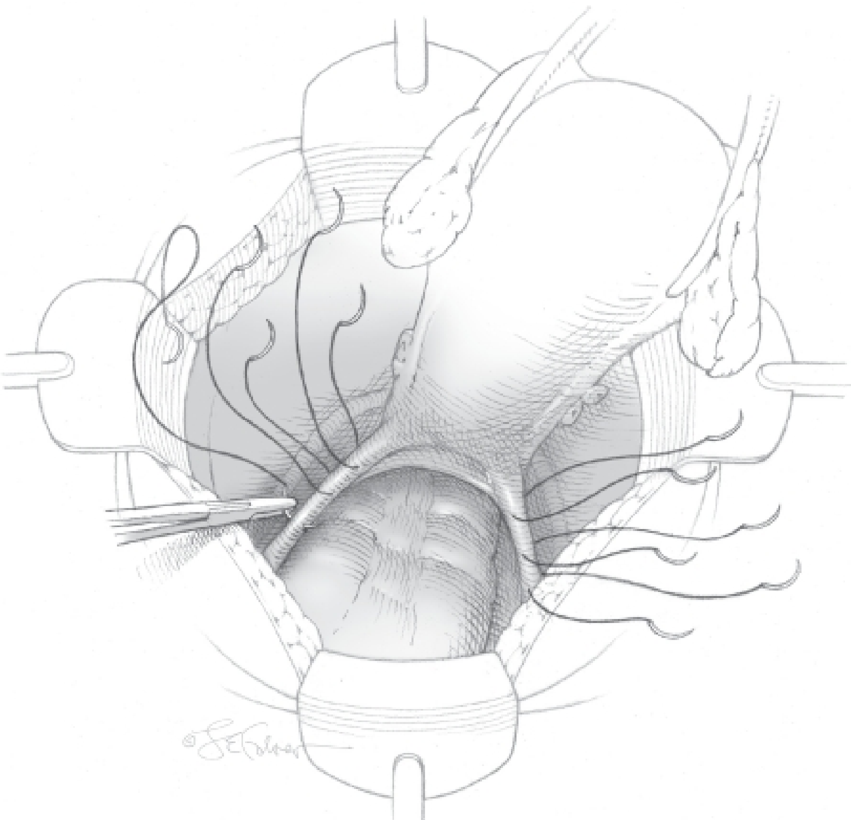
2. **Incision.** This surgery can be performed through a vertical low transverse or Pfannenstiel incision. After the abdomen is opened, a self-retaining retractor is placed and the bowel is packed from the operative field. In most cases, if hysterectomy is planned, then USLS is performed at completion of the abdominal hysterectomy.

3. **Identification of the Ureters.** The ureters are identified bilaterally because of an increased risk of ureteral injury while suturing the uterosacral ligaments.

4. **Identification of Uterosacral Ligaments.** Prior to beginning the hysterectomy, the surgeon should identify the uterosacral ligaments by applying contralateral upward traction to the uterine fundus (Fig. 42-18.1). With this technique, the uterosacral ligaments are placed on stretch and can be identified medial and posterior to the ischial spines.

   Three double-armed sutures of 2-0 permanent suture are placed 1 cm apart in each uterosacral ligament and held (Fig. 42-18.1). This is the step of greatest risk to the ureters. However, it should be emphasized that if sutures are placed medial and posterior to the ischial spines, the ureters will not be in jeopardy. For this reason, an EES sizer may be placed rectally to identify the lateral rectal wall and aid in medial placement of the sutures.

FIGURE 42-18.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

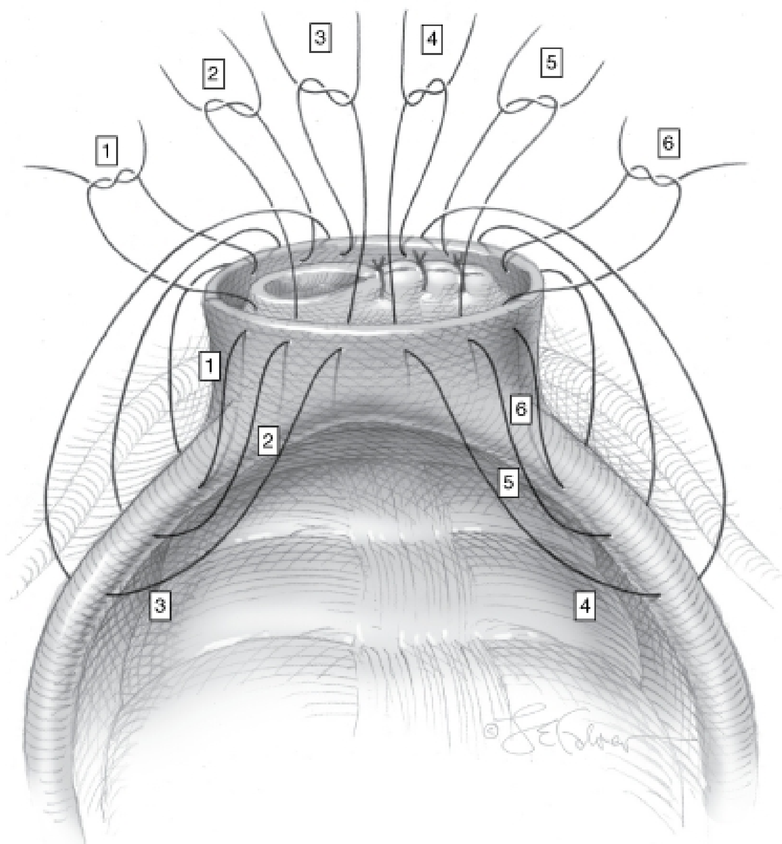
Uterosacral ligaments suture placement.

5. **Hysterectomy.** If hysterectomy is planned, it is now completed, but the cuff is left open. A purse-string suture of 2-0 delayed-absorbable suture is placed 1.5 cm from the edge of the cuff in the vaginal epithelium to close the vaginal apex. This step will prevent many cases of erosion of permanent USLS sutures through the vaginal epithelium.

6. **Suture Placement.** Six sutures are placed equidistant along the horizontal length of the vaginal cuff (Fig. 42-18.2). These sutures are place through the vaginal wall's fibromuscular layer above the prior purse-string. From both sides, the most cephalad sutures are placed through the horizontal midpoint of the vaginal cuff. One arm of the each suture is placed through the posterior fibromuscular layer of the vaginal wall, whereas the other arm sutures the anterior wall. The middle sutures (sutures 2 and 5) are placed next in a similar fashion. Lastly, the angle sutures (sutures 1 and 6) are placed at the cuff angles through the fibromuscular layers of the anterior and posterior vaginal walls.

   At this point, knots are secured starting with most medial sutures (sutures 3 and 4) and ending with the most lateral (sutures 1 and 6). This suturing order may prevent suture bridges in the lateral sutures. Care must be taken to firmly secure all knots and to confirm that the vaginal wall is directly approximated to the uterosacral ligaments (Fig. 42-18.3).

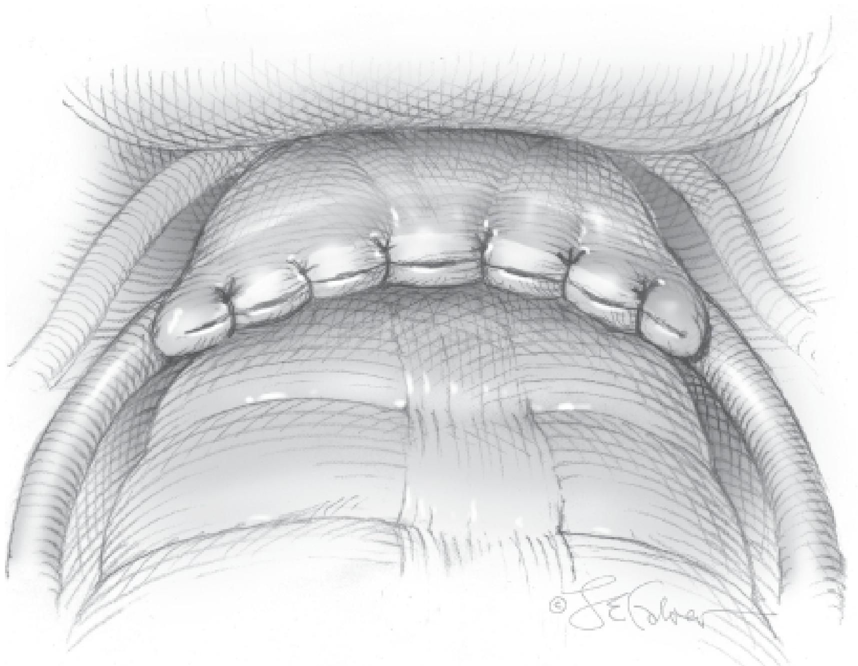
FIGURE 42-18.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Vaginal cuff suture placement.

FIGURE 42-18.3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

All sutures secured.

7. **Cystoscopy.** Cystoscopy is performed following intravenous administration of indigo carmine to document ureteral patency. After cystoscopy, vaginal examination may be performed to assess the need for addition prolapse repair of the anterior and posterior vaginal walls.

8. **Incision Closure.** The abdomen is closed in a standard fashion (see Sections 41-1, Midline Vertical Incision and 41-2, Pfannenstiel Incision).

9. **Concurrent Procedures.** If necessary, prior to incision closure, a paravaginal defect repair (see Section 42-14, Abdominal Paravaginal Defect Repair) or abdominal anti-incontinence surgery may be performed. If posterior colporrhaphy or vaginal anti-incontinence surgery is required, these will follow incision closure.

Postoperative

Following USLS, postoperative care follows that for any major abdominal surgery. Hospitalization typically varies from 2 to 4 days, and return of normal bowel function and febrile morbidity usually dictates this course. Postoperative activity in general can be individualized, although intercourse usually is delayed until after assessment of the vaginal cuff at 4 to 6 weeks following surgery. Catheter maintenance will vary and depends on whether or not anti-incontinence procedures were performed.

Suture erosion with granulation tissue can be a short- or long-term complication. As discussed in Sections 42-17, Abdominal Sacrocolpopexy, patients will present with either an asymptomatic permanent suture seen at the vaginal apex or granulation tissue. Generally, these sutures can be removed in the office. However, if sutures are asymptomatic and difficult to remove, they may remain.

42-19 VAGINAL UTEROSACRAL LIGAMENT SUSPENSION

Vaginal uterosacral ligament suspension (USLS), also called *high uterosacral ligament vault suspension,* is a popular approach to

vaginal apex suspension for women with symptomatic prolapse. In addition, this procedure is effective for repair of apical enteroceles.

During vaginal USLS, anterior and posterior aspects of the vaginal apex are attached to the uterosacral ligaments. As a result, continuity of the posterior and anterior vaginal walls is re-established, and the apex is resuspended.

Apical prolapse commonly develops concurrently with anterior and posterior compartment prolapse. Accordingly, vaginal USLS often is performed in conjunction with other surgeries to correct these defects, such as vaginal hysterectomy, anterior and posterior colporrhaphy, anti-incontinence procedures, and perineorrhaphy.

Preoperative

PATIENT EVALUATION

Prior to this procedure, patients with symptoms of urinary incontinence should undergo simple or complex urodynamic testing to determine the need for an anti-incontinence procedure (see Chap. 23, Diagnostic Testing). Patients without incontinence also should undergo testing with reduction of the prolapse to assess whether suspension of the apex will unmask incontinence. In patients with real or potential stress urinary incontinence, a concurrent anti-incontinence operation is performed.

Prolapse of the vaginal apex often coexists with other sites of prolapse along the vaginal vault. For this reason, a careful preoperative assessment should be performed, as described in Chapter 24, Perineal Examination. If identified, prolapse of the anterior or posterior vaginal walls can be repaired as needed concurrently with USLS.

CONSENT

The consenting process for USLS should include discussion of general risks associated with vaginal surgeries, as well as specific risks associated with the procedure. As with any prolapse repair, the most important long-term risk is recurrent prolapse. Although recurrence of vaginal apex prolapse is infrequent, prolapse of the anterior and posterior vaginal walls is common.

Urinary incontinence also may develop after USLS if an anti-incontinence procedure is not performed. Therefore, preoperative discussion of bladder function after surgery is essential. In addition, uterosacral ligament suspension does have a potential to shorten and fix the upper vagina. Therefore, women should be aware of the potential for postoperative dyspareunia. Additionally, nerve injury and subsequent neuropathy has been reported after USLS and should be discussed.

The ureters are at risk during placement of uterosacral ligament suspension sutures. In the literature, the risk varies and in some series has been reported in up to 25 percent of patients. This complication appears to be related to surgeon experience. Knowledge of anatomy and correct suture placement should minimize this risk.

Permanent sutures are recommended for apical suspension. As a result, suture erosion and nonhealing granulation tissue can develop frequently. Therefore, efforts should be made to avoid suturing through the vagina epithelium.

PATIENT PREPARATION

Bowel preparation and evacuation of the rectum are recommended and are administered the evening prior to surgery (see Table 39-10). In addition, antibiotic prophylaxis is provided prior to surgery.

Intraoperative

Surgical Steps

1. **Anesthesia and Patient Positioning.** Vaginal USLS typically is performed under general or regional anesthesia. The patient is placed in dorsal lithotomy position using candy-cane stirrups. Examination under anesthesia is performed to assess degree of prolapse and confirm the need for surgeries planned. The vagina and abdomen are surgically prepared, and a Foley catheter is placed.

2. **Incision.** The initial incision can be made in a variety of ways. If in the context of vaginal hysterectomy, the vaginal cuff is already open, and uterosacral ligaments are simply identified. However, if the procedure is performed in a woman who previously has undergone hysterectomy, then a vaginal incision can be created in one of two ways. First, a midline incision

may be made in the posterior vaginal wall beginning at the perineum, and dissection proceeds cephalad to the vaginal apex. With this technique, vaginal epithelium is dissected off the vaginal wall. An enterocele sac is identified and entered.

Alternatively, an elliptical incision can be made directly over the entercoele sac at the vaginal apex. The vaginal epithelium is excised in this region, and the enterocele sac is identified and entered.

3. **Packing and Retraction.** A key step of this procedure requires that bowel must be adequately packed away so that high uterosacral sutures can be placed without bowel injury. Several moist laparotomy sponges are placed in the cul-de-sac of Douglas and hollow of the sacrum to elevate bowel from the operative field.

   Additionally, two Breisky-Navratil retractors are positioned (see Fig. 40-20). One reflects the rectum to the contralateral side of the ligament being sutured. A second is used to reflect remaining bowel. At times, a third may be necessary to clear the field adequately.

4. **Identification of Uterosacral Ligaments.** Initially, the ischial spines are palpated, and the uterosacral ligaments are found medial and posterior to the spines and lateral to the rectum. Additionally, Allis clamps may be placed on the posterior vaginal wall at the apex. If traction is applied, uterosacral ligaments become taut and are identified more easily by their cord-like texture.

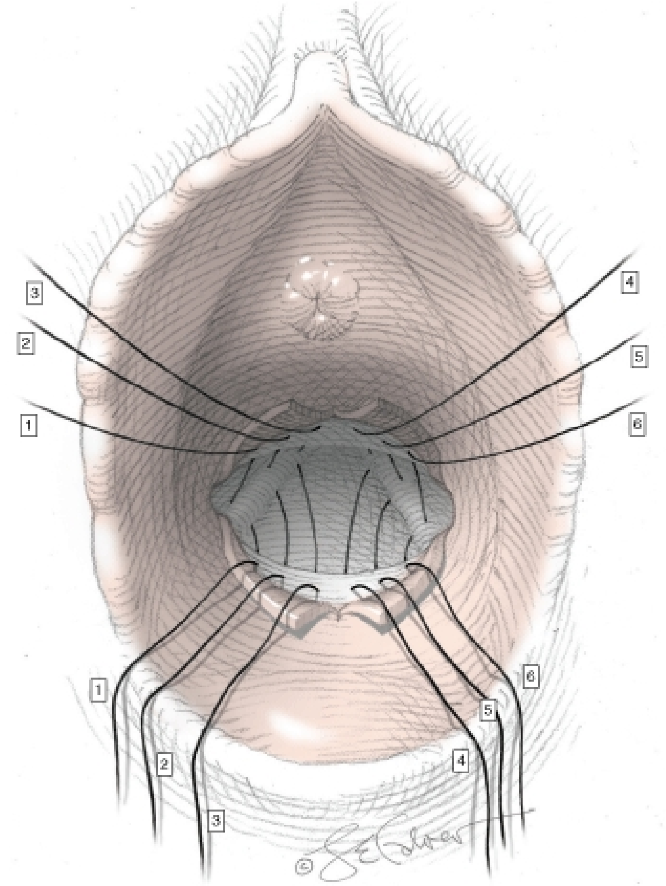
5. **Placement of Sutures in the Uterosacral Ligament.** Beginning at the level of the ischial spines and progressing cephalad, a surgeon places three double-armed 2-0 permanent sutures approximately 1 cm apart in each uterosacral ligament (Figs. 42-19.1 and 42-19.2). Following the normal path of these ligaments, the most caudal sutures will be most medial.

   To avoid ureteral injury, it is of vital importance that sutures be placed medial and posterior to the ischial spines. In addition, ureteral injury is averted by directing needles medially during suturing. Although this will place sutures near the lateral border of the rectum, bowel injury is avoided by retraction with a Breisky-Navratil retractor.

   In some instances, uterosacral ligaments are attenuated and difficult to identify distinctly. In these circumstances, suturing may proceed by placing stitches in the expected anatomic area for these ligaments.

   Hematomas may form occasionally following inadvertent laceration of the lateral rectal veins. Should this occur, application of pressure with a sponge stick typically will control bleeding.

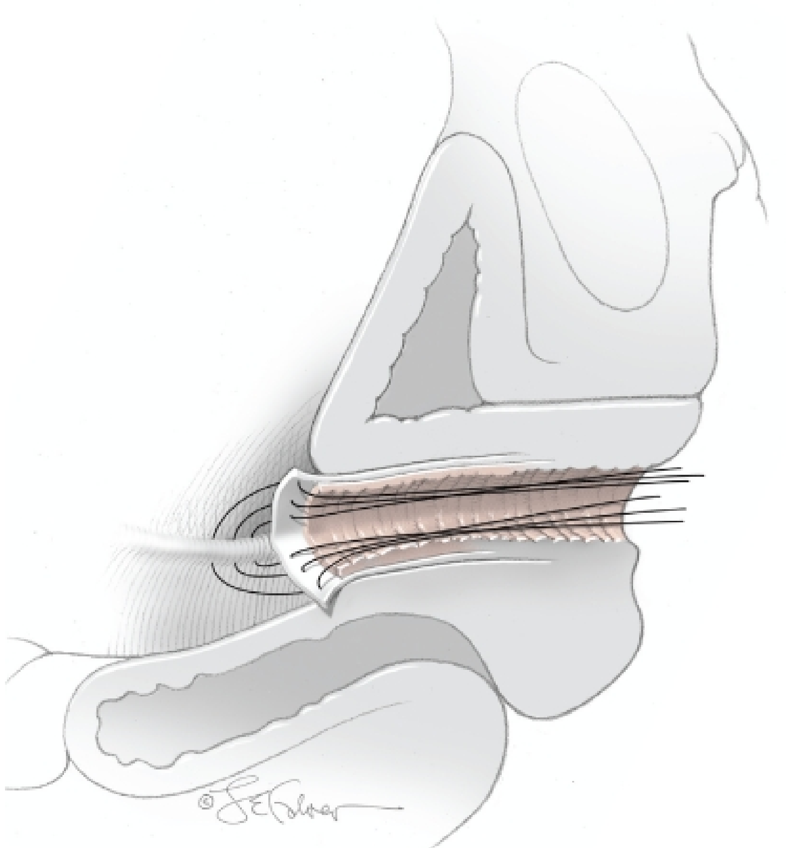
FIGURE 42-19.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Vaginal view of sutures placed into uterosacral ligaments.

FIGURE 42-19.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Lateral view of sutures placed into the left uterosacral ligament.

6. **Cystoscopy.** After all six stitches are placed and tied, 1/2 to 1 ampule of indigo carmine is administered intravenously. Cystoscopy is performed to exclude ureteral injury prior to proceeding with the remaining surgical steps.

7. **Placement of Sutures in the Vaginal Wall.** The most distal suspensory suture on each side is sown to the most lateral portion of the anterior and posterior fibromuscular layers at the corner of the vaginal apices. The suture cephalad to this first one is placed more medially, through the vaginal wall. Finally, the most cephalad suture is placed in the midline of the anterior and posterior fibromuscular layers. Tangling of sutures is common. Thus, sutures may be tagged, numbered, and attached to surgical drapes.

   Vaginal packing is removed, and sutures are tied. The most medial sutures are tied first. As knots are secured, the vaginal walls should be brought into immediate contact with the uterosacral ligaments to avoid bow-stringing, which can lead to bowel obstruction.

8. **Closure of the Vaginal Cuff.** The vaginal cuff is reapproximated in a running fashion with 2-0 delayed-absorbable suture.

Postoperative

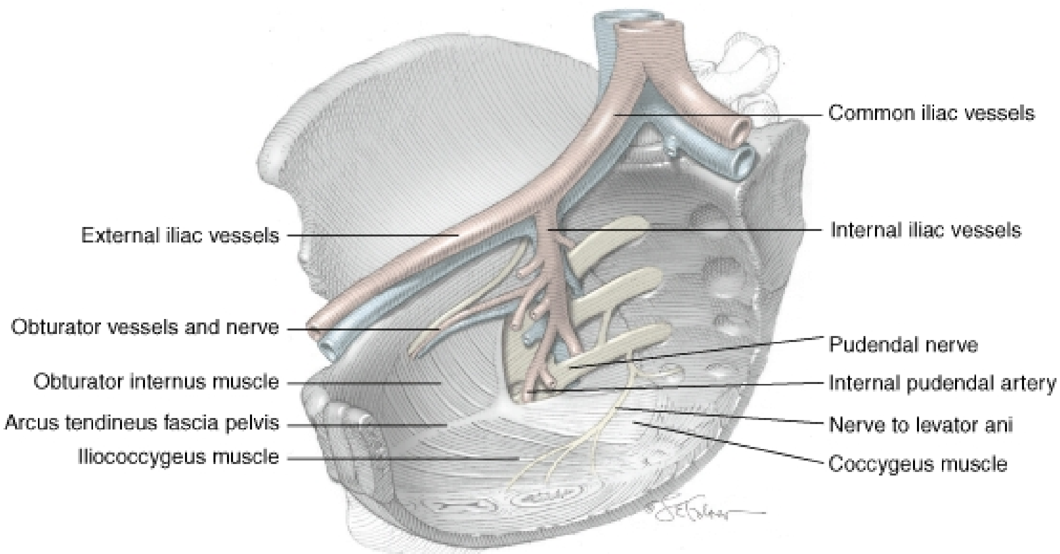
Following USLS, postoperative care follows that for any vaginal surgery. Postoperative activity in general can be individualized, although intercourse usually is delayed until after assessment of the vaginal cuff at 4 to 6 weeks following surgery. Catheter maintenance will depend on whether or not anti-incontinence procedures were performed.

42-20 SACROSPINOUS LIGAMENT FIXATION

Prolapse of the vaginal apex may be corrected by several procedures. One vaginal approach, termed *sacrospinous ligament fixation,* uses the strength of the sacrospinous ligament to resuspend the apex. Stretching from the ischial spine to the lateral surface of the sacrum's inner hollow, this ligament is a tough, fibrous aponeurosis that lies within the body of the coccygeus muscle (Fig. 42-20.1). The great size and tensile strength of this ligament allow it to serve as an excellent support for suspensory surgery.

Although effective in correcting apical prolapse, sacrospinous ligament fixation compares less favorably with abdominal sacrocolpopexy (Benson, 1996; Maher, 2004). However, sacrospinous ligament fixation averts abdominal surgery and is associated with shorter operating times and quicker recovery. For these reasons, it often provides a superior choice for women with other significant health problems. Additionally, the vaginal approach allows other concurrent support defects to be repaired vaginally at the same time as fixation. Compared with other vaginal approaches for vault suspension, success rates are comparable (Maher, 2001).

FIGURE 42-20.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Sacrospinous ligament and surrounding pelvic anatomy.

Preoperative

PATIENT EVALUATION

Prior to sacrospinous ligament fixation, women with symptoms of urinary incontinence should undergo urodynamic testing to determine the need for an adjunctive anti-incontinence procedure (see Chap. 23, Diagnostic Testing). Patients without incontinence also should undergo testing with reduction of the prolapse to assess whether suspension of the apex will unmask incontinence. In women with real or potential stress urinary incontinence, a concurrent anti-incontinence operation is indicated.

Prolapse of the vaginal apex often develops with prolapse at other sites along the vaginal vault. Accordingly, careful preoperative assessment should be performed, as described in Chapter 24, Perineal Examination. If identified, prolapse of the anterior or posterior vaginal walls can be repaired as needed concurrently with sacrospinous ligament fixation.

CONSENT

For most women, sacrospinous ligament fixation is effective in preventing recurrent apical prolapse, and success rates range from 70 to nearly 100 percent (Cruikshank, 2003; Lantzsch, 2001; Maher, 2004). The procedure is safe and associated with low rates of

serious complications. Significant hemorrhage requiring transfusion is uncommon and typically results from injury to the pudendal, inferior gluteal, or inferior rectal vessels. Rates of long-term nerve injury similarly are low, and injury typically involves the pudendal or inferior gluteal nerves (Sagsoz, 2002). Rarely, life-threatening infections such as necrotizing fasciitis and ischiorectal fossa abscess may develop (Hibner, 2005; Silva-Filho, 2005).

As with other pelvic reconstructive surgeries, new pelvic support defects may follow sacrospinous fixation, and rates for development of any support defect range from 15 to 40 percent (Paraiso, 1996; Shull, 1992). During fixation, the vagina's long axis is redirected posteriorly. As this axis is lowered, the anterior compartment of the pelvis widens and lies vulnerable to increased intra-abdominal pressures. Accordingly, anterior compartment defects (cystoceles) develop postoperatively in 10 to 40 percent of patients (Lantzsch, 2001; Paraiso, 1996). As a result, increased rates of stress urinary incontinence also may be noted.

Concern is often expressed regarding shortening of the functional vaginal length by this procedure, and postoperative lengths approximate 8 cm (Given, 1993). Despite a resulting shorter vaginal length when compared with an abdominal approach for suspension, de novo dyspareunia is infrequent. Indeed, for many women, replacement of the vagina to a more anatomic location leads to improved satisfaction with intercourse following surgery (Maher, 2004).

PATIENT PREPARATION

The risk of intraoperative rectal injury is not uncommon with sacrospinous ligament fixation. For this reason, bowel preparation, is performed the evening prior to surgery (see Table 39-10).

As with most vaginal surgery, because of the risk posed by the normal vaginal flora for postoperative wound cellulitis and abscess, preoperative antibiotics are warranted. Typical agents include first- or second-generation cephalosporins.

Intraoperative

SURGICAL INSTUMENTS

Placement of sutures into the sacrospinous ligament can be performed with a variety of ligature carriers, including the Dechamps ligature carrier, Miya hook, Capio ligature carrier (Boston Scientific, Boston, MA), and the EndoStitch (United States Surgical, Norwalk, CT). Using the Deschamps ligature carrier, the surgeon threads the suture through an eye at the needle-shaped tip of the carrier. Arcs and curves constructed into the instrument aid of suture placement into the ligament. Disadvantages to this device, however, include the relative thickness of the needle tip, which can add difficulty in perforating the ligament. Alternatively, Miyazaki (1987) described 74 cases using the Miya hook. This device aids in passage through the ligament. However, there is less control of the needle and suture because the device has moving parts. These first two offer additional cost advantages because they are reusable. With adequate exposure, another reusable device that can be used easily is a long needle driver.

Alternatively, disposable devices have become popular, in particular, the Capio ligature carrier (Boston Scientific, Natick, MA). This device is easier to manipulate than the Miya hook, and the needle is well controlled at all times.

Surgical Steps

1. **Anesthesia and Patient Positioning.** After general anesthesia has been administered, the patient is placed in dorsal lithotomy position, the vagina is surgically prepared, and a Foley catheter is placed. Initially, vaginal vault prolapse is reduced to place the vagina in a normal anatomic position. Enterocele or cystocele repairs, if planned, should precede sacrospinous ligament fixation.

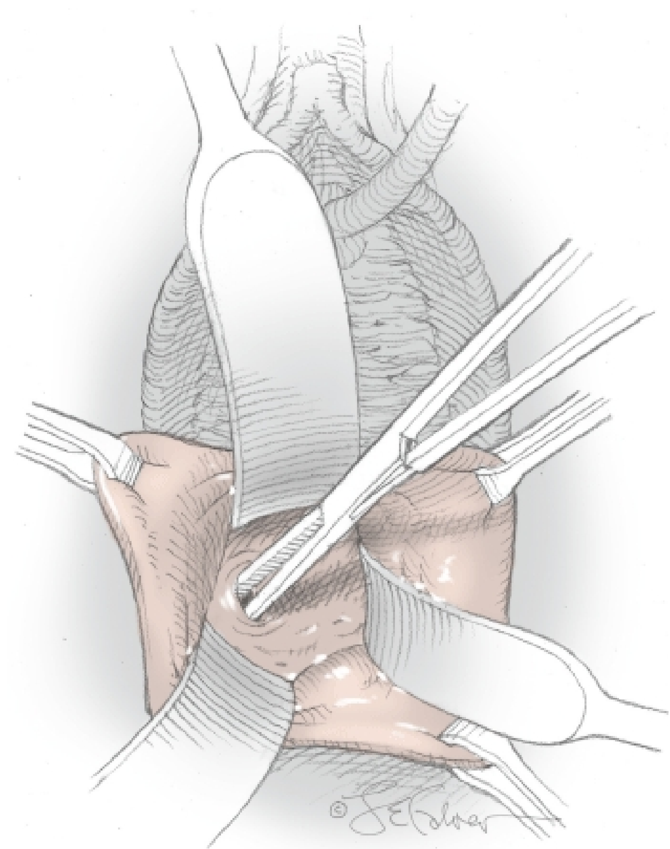
2. **Unilateral or Bilateral Fixation.** Although the vaginal apex may be attached to either one or both sacrospinous ligaments, in most instances, unilateral fixation gives sufficient support. The right ligament is preferred because most surgeons are right handed. Additionally, fixation to the right side avoids anatomic difficulties posed by the rectum.

   Alternatively, bilateral fixation has been advocated as a method to maintain the vaginal apex in a midline plane and to provide superior durability because of additional support given by two ligaments (Cespedes, 2000). Clear benefits to bilateral compared with unilateral fixation have not, however, been evaluated in clinical trials, and greater rates of postoperative anterior compartment prolapse have been noted following bilateral fixation (Pohl, 1997).

3. **Access to the Sacrospinous Ligament.** The sacrospinous ligament is accessed through the pararectal space. Entering the pararectal space permits close proximity to the ligament with minimal dissection.

4. **Entry into Pararectal Space.** Using a pararectal approach, the surgeon sharply incises the posterior vaginal wall and separates it from the underlying rectum, as described in Section 42-15, Posterior Colporrhaphy. These steps reveal the perirectal fascia, and the rectal pillars are seen on either side of the rectum (Fig. 42-20.2). The right rectal pillar is entered sharply by placing and opening a hemostat at the level of the ischial spine. This blunt dissection permits entry into the pararectal space.

FIGURE 42-20.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Entry into pararectal space.

5. **Retractor Positioning.** Breisky-Navratil retractors are positioned within the pararectal space (see Fig. 40-20). The first, positioned anteriorly, lifts pelvic contents away from the surgical site. The second is place to the patient's left and retracts the rectum. The last is held inferiorly and parallel to the ligament.

6. **Ligament Dissection.** After entering the right pararectal space, the ischial spine is located digitally, and the path of the sacrospinous ligament is traced medially. Blunt dissection with fingertips removes loose adventitial tissue overlying the midportion of the ligament.

During dissection within the pararectal space or retraction of the rectum, vessels in the area may be lacerated and most commonly include branches of the inferior rectal vessels. Hemorrhage in this area is often best managed with packing a sponge into the area and holding pressure.

7. **Ligature Placement.** Following dissection, the ligament is grasped with a Babcock clamp at a spot approximately 2.5 cm medial to the ischial spine. This transforms the flat ligament into a thicker, more rounded structure and often allows the lateral retractor to be removed for greater visualization and mobility of the ligature carrier.

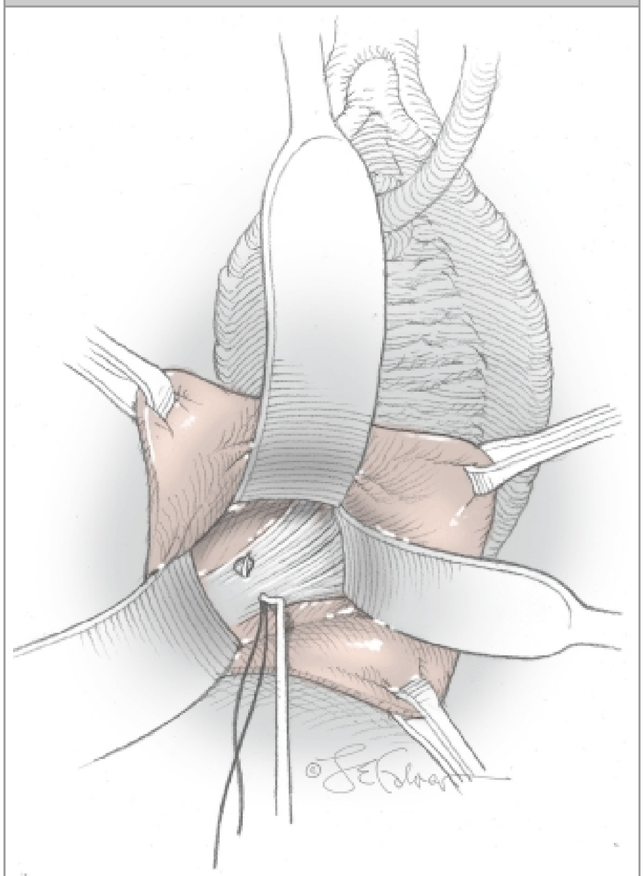
   A ligature carrier is loaded with 0-gauge permanent suture. Although erosion of sutures through the vaginal apex postoperatively has been noted, use of permanent sutures increases repair durability (Chapin, 1997). In addition, use of monofilament sutures to lower infection risks in this procedure has been advocated (Hibner, 2005).

   The pudendal and inferior gluteal vessels and nerves lie behind the sacrospinous ligament and may be injured during sacrospinous ligament fixation. For this reason, sutures should be placed 2.5 to 3 cm medial to the ischial spine and are not placed completely through the entire thickness of the ligament (Sagsoz, 2002; Verdeja, 1995).

   If a vessel is lacerated and immediate isolation and ligation are not possible, the area of hemorrhage may be packed with laparotomy sponges and pressure held for several minutes. As sponges then are removed gradually, a site of laceration can be identified and clipped with a vascular clip or ligated.

   A ligature carrier is held in the surgeon's right hand, and the tip of the driver is placed toward the inferior edge of the ligament (Fig. 42-20.3). The tip then pierces the ligament with a clockwise motion of the carrier.

FIGURE 42-20.3



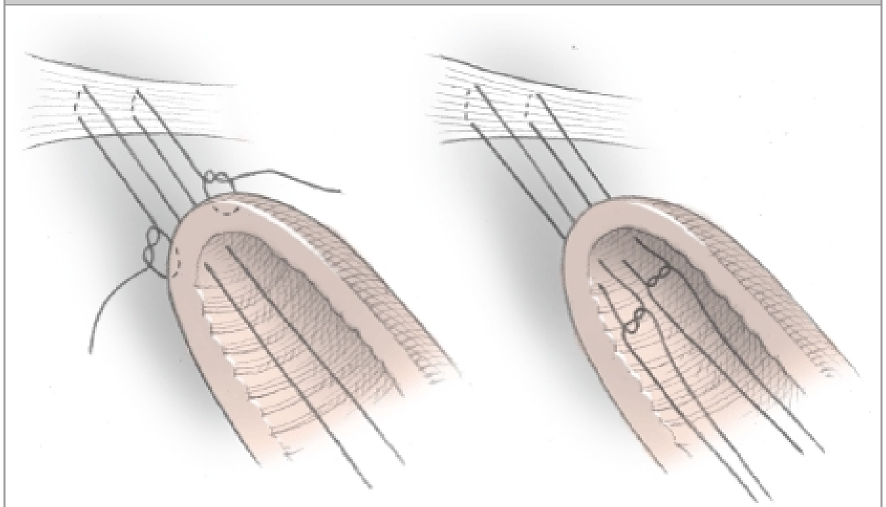
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Ligature placement.

8. **Vaginal Apex Suturing.** The suture loop is snagged with a nerve hook and pulled into the vagina. The loop is cut, thereby leaving two separate sutures within the ligament. This allows placement of two sutures with only one carrier pass and thus minimizes adjacent tissue injury. Two pulley stitches then are placed in the vaginal apex (Fig. 42-20.4).

   With the Michigan modification of this procedure, two sutures are placed through the ligament, allowing for four sutures with two ligament passes (Figs. 42-20.5 and 42-20.6). These sutures then are used to attach the anterior and posterior vaginal walls to the sacrospinous ligament.

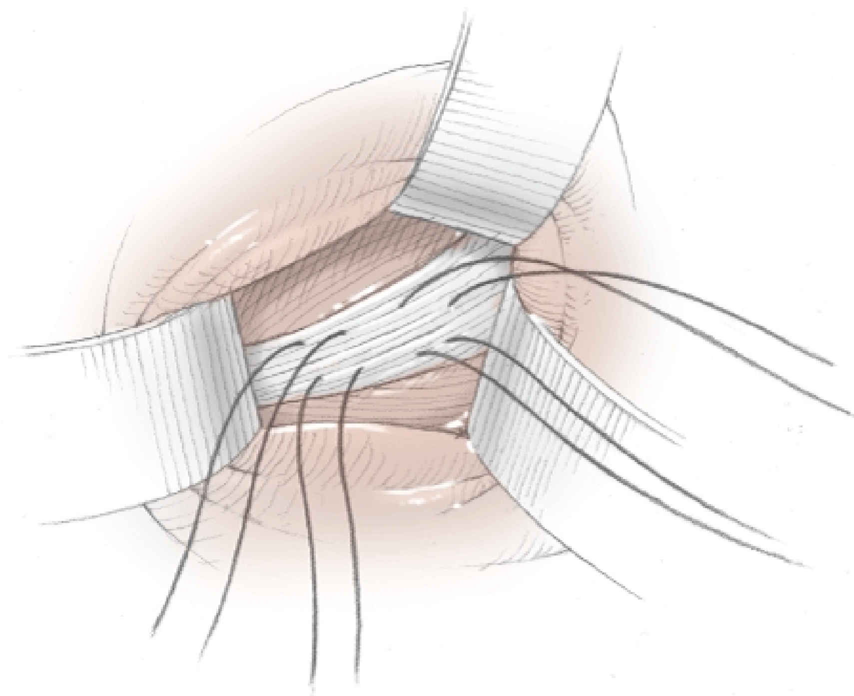
FIGURE 42-20.4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Vaginal apex pulley stitches.

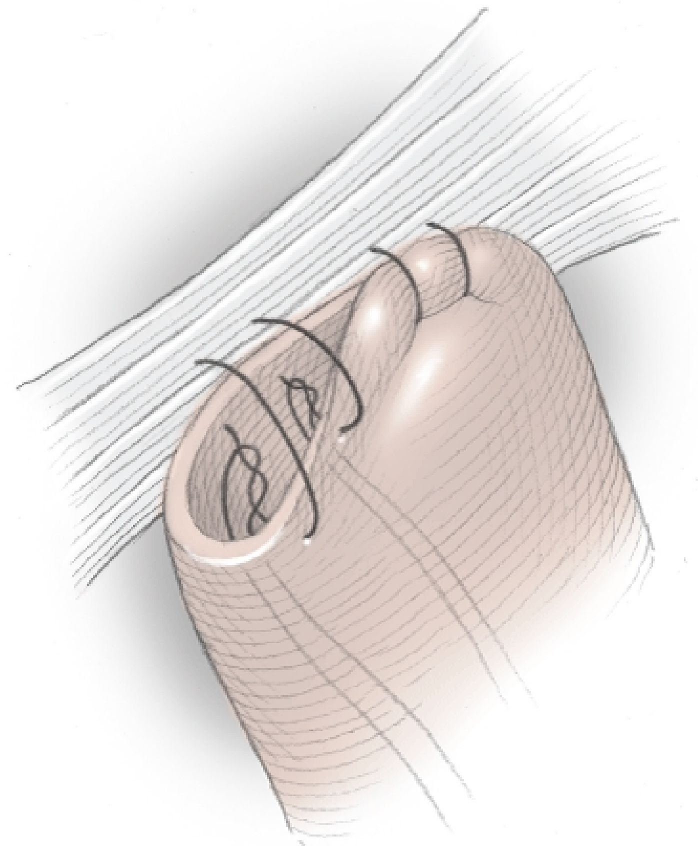
FIGURE 42-20.5



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Michigan modification.

FIGURE 42-20.6



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Vaginal apex approximated to ligament.

9. **Closure of Posterior Vaginal Wall and Pararectal Space.** The proximal posterior vaginal wall is reapproximated with a running closure using 2-0 delayed-absorbable suture. The pararectal space then is closed similarly.

10. **Vault Resuspension.** The pulley stitches then are tightened, bringing the vaginal apex directly to the ligament. The remainder of the vaginal wall then is closed in a running fashion using 2-0 delayed-absorbable suture.

Postoperative

Following surgery, patients may ambulate on the first postoperative day, and diet may be advanced as tolerated. Mild buttock pain may follow surgery and resolves typically in days to months. Such neuralgia is common following surgery, and Lantzsch and associates (2001) found a rate of 8 percent in their series. Nonsteroidal anti-inflammatory drugs in this setting may be helpful.

Occasionally, a patient may complain of severe pain and display sensory or motor neurologic symptoms or both (see Chap. 40, Sciatic Nerve). If motor symptoms are present, the chance for nerve entrapment of sciatic nerve or its branches is great. These women should undergo exploration of the pararectal space and removal of entrapping sutures.

42-21 MCCALL CULDOPLASTY

McCall culdoplasty is performed at the time of vaginal hysterectomy to close the cul-de-sac, add support to the posterior vaginal apex, and possibly prevent enterocele formation. The main difference between this procedure and Halban and Moschcowitz

culdoplasty methods lies in its vaginal approach. No data support the superior efficacy of one when these three are compared. Thus, the choice of procedure should be based on the approach planned for hysterectomy and on other concurrent surgeries.

Culdoplasty is suggested to prevent enterocele formation and vaginal vault prolapse. However, if significant vaginal apex prolapse or enterocele is already present, then either sacrospinous ligament fixation or vaginal uterosacral ligament suspension of the vaginal vault is preferred.

Preoperative

PATIENT EVALUATION

McCall culdoplasty generally is performed following vaginal hysterectomy in women with enterocele or preventively in those without. Because the degree of pelvic organ prolapse will dictate the reconstructive surgeries planned, a thorough prolapse evaluation should be performed, as described in Chapter 24, Perineal Examination.

CONSENT

As with any pelvic reconstructive surgery to correct prolapse, the risk of enterocele formation or recurrence should be discussed. Risks of ureteral and bowel injury, although low, should be included in the consenting process.

PATIENT PREPARATION

Postoperative vaginal cuff cellulitis and urinary tract infection may follow hysterectomy, and patients typically receive antibiotic prophylaxis with either a first- or second-generation cephalosporin. Alternatively, clindamycin may be used. The risk of bowel injury is low. However, bowel preparation is recommended prior to surgery to evacuate the rectum and thus decrease contamination should proctotomy occur.

Intraoperative

Surgical Steps

1. **Anesthesia and Patient Positioning.** McCall culdoplasty typically is performed under general anesthesia, although epidural or spinal regional methods may also be appropriate. The patient is placed in a high lithotomy position in candy-cane stirrups. The vagina is surgically prepared, and a Foley catheter is inserted. Vaginal hysterectomy is completed as described in Section 41-20, Vaginal Hysterectomy, but the vaginal cuff is left open for completion of the culdoplasty.

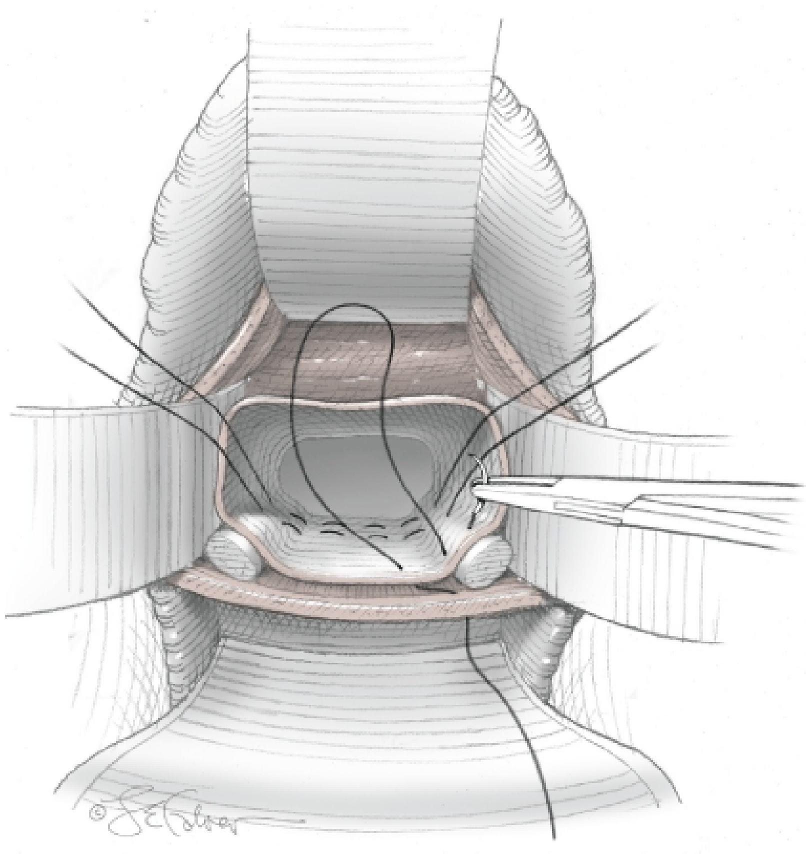
2. **Packing.** After vaginal hysterectomy, a moist pack is placed into the posterior cul-de-sac to prevent descent of bowel or omentum into the operative field.

3. **Identification of Uterosacral Ligaments, Rectum, and Ureters.** The uterosacral ligaments, which were tagged previously during vaginal hysterectomy, are placed on lateral traction to define the course of the ligaments to the pelvic sidewall. Alternatively, Allis clamps can be placed on the posterior vaginal wall and traction applied to identify the uterosacral ligaments. The ureter always lies lateral to the uterosacral ligament, and although it may not be visualized per se, placement of sutures medial to the ligament will avoid ureteral injury. Additionally, rectal examination should delineate the lateral borders of the rectum to avoid needle stick injury to the bowel.

4. **Suture Placement.** The first internal 2-0 permanent suture is placed proximally into one uterosacral ligament, taking care to always direct the needle toward the midline to avoid ureteral injury (Fig. 42-21.1). Subsequent serial bites are placed 1 cm apart across the rectosigmoid colon's serosa to reach and penetrate the opposite ligament. This suture is left untied. Additional caudal rows of sutures are similarly placed 1 cm apart between the uterosacral ligaments, extending caudally toward the vaginal cuff. Depending on the size and depth of the cul-de-sac, the number of rows will vary.

   Following completion of the internal suture rows, one external suture row is placed using 2-0 delayed-absorbable suture and incorporates the posterior vaginal wall. This suture is placed initially through the full thickness of the posterior vaginal wall and into the uterosacral ligament. Progressive left to right bites then are taken serially through the rectosigmoid serosa to reach the opposite uterosacral ligament. Finally, the suture enters the opposite uterosacral ligament and exits through the full vaginal wall thickness to re-enter the vagina (Fig. 42-21.2).

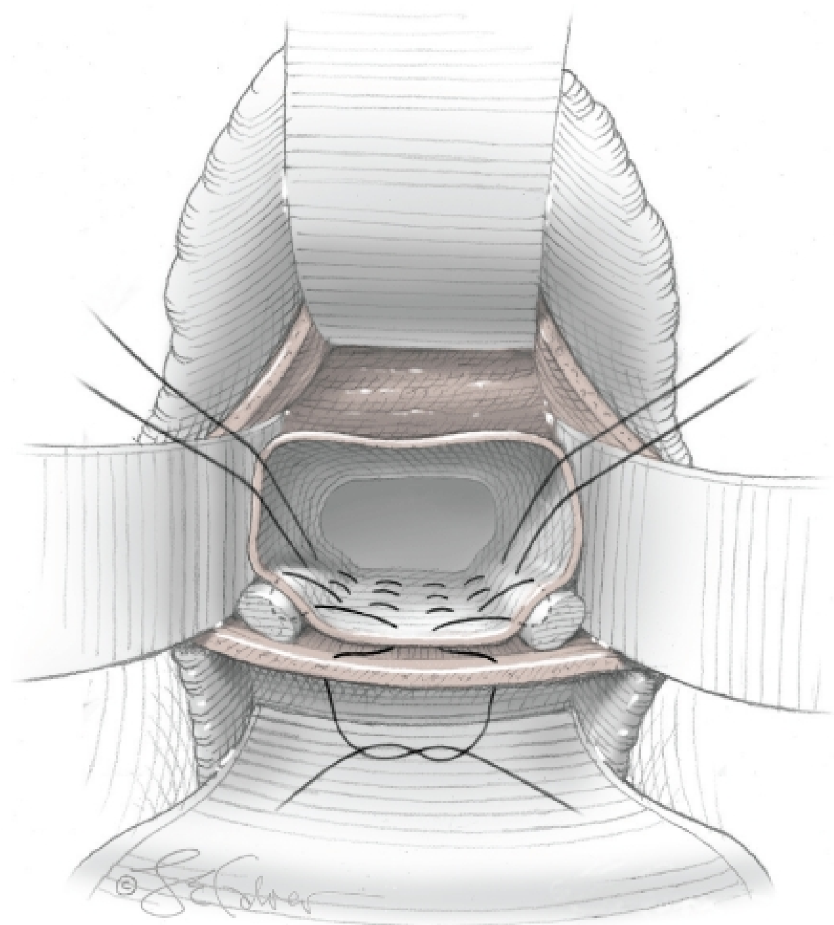
FIGURE 42-21.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Uterosacral ligament suture placement.

FIGURE 42-21.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Suture reenters the vagina prior to securing.

5. **Suture Tying.** The sutures are tied sequentially beginning with the most proximal sutures and progressing caudally.

6. **Cystoscopy.** Because of the proximity of suture placement to the ureters, cystoscopy should be considered to document ureteral patency.

7. **Vaginal Cuff Closure.** On completion of McCall culdoplasty, the remaining steps of vaginal hysterectomy will follow, as described in Section 41-20, Vaginal Hysterectomy (Step 11).

Postoperative

Following vaginal hysterectomy and McCall culdoplasty, postoperative care follows that for most vaginal surgeries. Hospitalization typically varies from 1 to 3 days, and return of normal bowel and bladder function usually dictates this course. Postoperative activity in general can be individualized, although intercourse usually is delayed until after the first postoperative visit at 4 weeks to allow inspection of vaginal cuff healing.

42-22 ABDOMINAL CULDOPLASTY PROCEDURES

Culdoplasty techniques are used to obliterate the cul-de sac of Douglas and prevent herniation of small bowel into the vaginal wall. Thus, these procedures traditionally have been thought of as appropriate for repair and prevention of enteroceles. However, evidence-based studies have not borne out these benefits, and current concepts of specific pelvic support defect repair have decreased the popularity of culdoplasty. Nevertheless, this procedure is still performed commonly and may have value when performed in conjunction with other prolapse procedures.

Included in this group are the Moschcowitz and Halban procedures. With these, permanent sutures are used to close the cul-de-sac, and procedures vary based on the orientation of suture placement. Either the Halban or Moschcowitz procedure may be selected, and the decision is based on surgeon's preference and concurrent abdominal or vaginal pathology. No studies have been completed that compare these techniques.

Preoperative

PATIENT EVALUATION

Culdoplasty procedures typically are performed with other prolapse surgeries. Thus, thorough pelvic organ prolapse evaluation should be performed, as described in Chapter 24, Perineal Examination. All sites of prolapse should be considered when planning surgical correction. Depending on the type of prolapse present, urodynamic testing also may be indicated to exclude potential stress urinary incontinence.

CONSENT

As with any pelvic reconstructive surgery to correct prolapse, the risk of enterocele recurrence following abdominal culdoplasty should be discussed. Additionally, risks of ureteral and bowel injury should be included in the consenting process. During Halban and Moschcowitz culdoplasty, the rectosigmoid is plicated to the posterior vaginal wall. Accordingly, defecatory dysfunction and technical difficulty in performing subsequent colonoscopy have been reported following these procedures.

PATIENT PREPARATION

Because of the potential for bowel injury, bowel preparation is performed the evening prior to surgery (see Table 39-10). In addition, antibiotic prophylaxis is administered immediately before surgery.

Intraoperative

Surgical Steps

1. **Anesthesia and Patient Positioning.** Abdominal culdoplasty typically is performed under general anesthesia, although regional techniques may also be used. The patient is positioned in a low lithotomy position with the legs in Allen stirrups and the thighs parallel to the ground. This positioning allows access to the vagina as well as normal abdominal laparotomy exposure. A Foley catheter is placed, and the abdomen and vagina are prepared for surgery.

2. **Surgical Incision.** Either a transverse or a vertical incision may be used for culdoplasty. Incision choice depends on concurrent surgeries planned (see Sections 41-1, Midline Vertical Incision and 41-2, Pfannenstiel Incision). A self-retaining retractor such as an O'Connor-O'Sullivan or Balfour retractor is placed, and concurrent surgeries such as hysterectomy or sacrocolpopexy are performed.

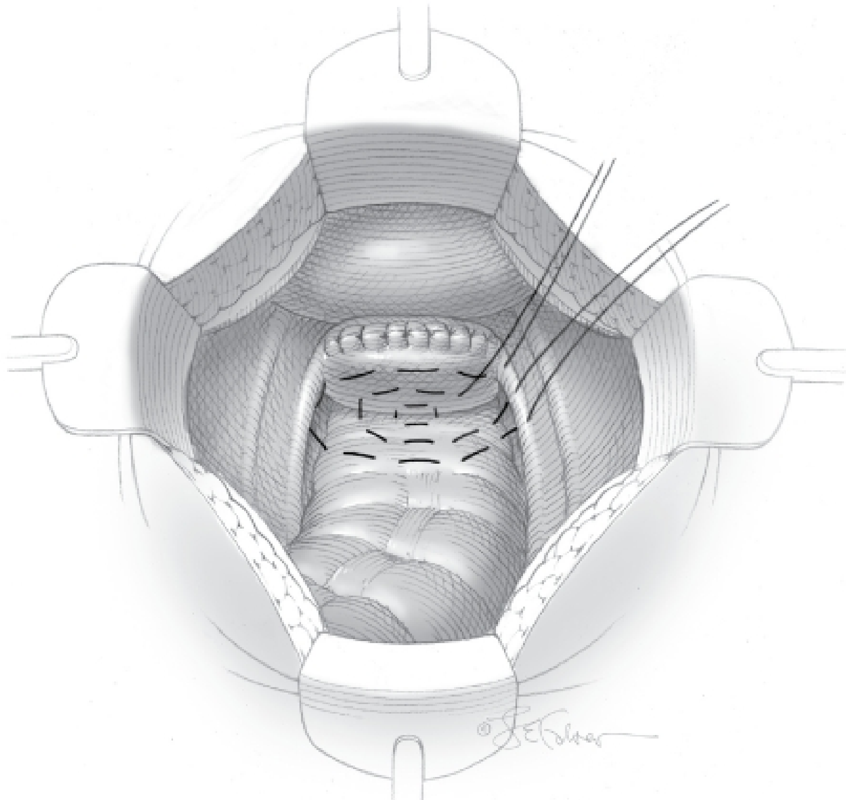
3. **Special Considerations.** Following completion of initial procedures, the cul-de-sac is exposed and evaluated for suture placement. Additionally, end-to-end anastomosis (EEA) sizers may be placed within the vagina or rectum to identify borders and allow correct suture placement. Prior to culdoplasty, both ureters should be re-identified.

   In the past, these procedures have focused on suturing peritoneal and serosal surfaces. However, a more effective approach incorporates deep bites into the muscularis of the vagina and sigmoid, taking care to avoid both bowel and vaginal lumens. During placement of rectosigmoid sutures, attempts should be made to avoid adjacent rectosigmoid veins because hematomas form commonly. If bleeding develops, direct vascular compression provides effective control in most instances.

4. **Halban Culdoplasty.** Several rows of sutures are placed longitudinally through the serosa and muscularis of the sigmoid (Fig. 42-22.1). Attention is given to avoiding entry into the lumen. The same sutures then are advanced through the

peritoneum of the deep cul-de-sac and up toward the apex of the posterior vaginal wall. As much of the cul-de-sac as possible should be obliterated, but to avoid ureteral injury, sutures never should be placed lateral to the uterosacral ligaments.

FIGURE 42-22.1

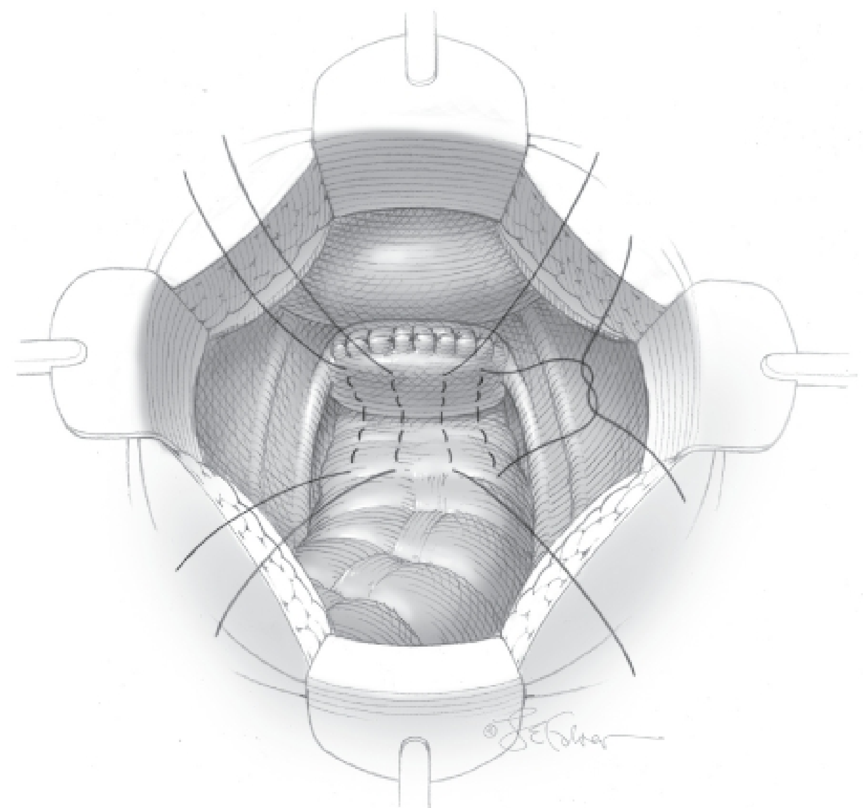


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Halban culdoplasty.

5. **Moschcowitz Culdoplasty.** Concentric sutures are placed in the cul-de-sac beginning at the base and are directed upward almost to the level of the vaginal apex (Fig. 42-22.2). During placement, sutures are placed through the posterior vaginal wall and then advanced through the right uterosacral ligament, the sigmoid colon muscularis, and finally, the left uterosacral ligament. The number of concentric rings required depends on the depth of the cul-de-sac, and usually three to four rings is sufficient. With this procedure, ureteral kinking should be avoided during suture tying.

FIGURE 42-22.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Moschcowitz culdoplasty.

6. **Cystoscopy.** Consideration should be given to performing cystoscopy after sutures are tied because of the potential risk of ureteral injury with culdoplasty procedures.

7. **Incision Closure.** The abdominal incision is closed as described in Section 41-1, Midline Vertical Incision or 41-2, Pfannenstiel Incision.

Postoperative

Following culdoplasty, postoperative care follows that for any major abdominal surgery. Hospitalization typically varies from 2 to 4 days, and return of normal bowel function usually dictates this course. Stool softeners should be administered because defecatory dysfunction can develop because of a change in the rectosigmoid angle. These may be continued as needed to maintain normal bowel function.

42-23 LEFORT PARTIAL COLPOCLEISIS

There are two basic approaches to the repair of vaginal vault prolapse: obliterative and reconstructive. Although reconstructive approaches recreate a functional vagina, obliterative procedures reach nearly 100 percent success rates in curing prolapse.

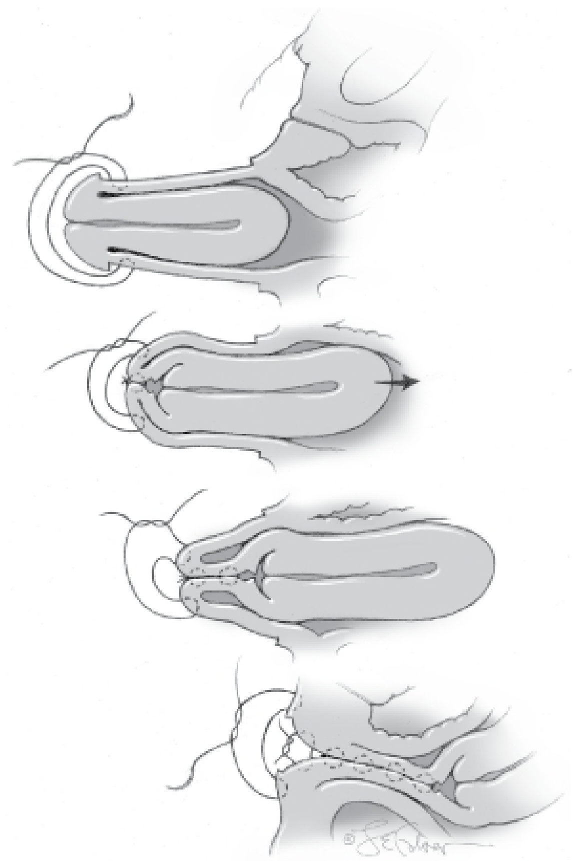
The Lefort partial colpocleisis is an obliterative vaginal procedure that approximates the anterior and posterior vaginal walls. This surgery effectively replaces the prolapsed vagina vault into the abdominal cavity in women with or without a uterus (Fig. 42-23.1).

The procedure is performed in women with significant prolapse of the uterus, vagina, and anterior and posterior vaginal walls beyond the hymen.

As opposed to complete colpocleisis, with Lefort partial colpocleisis, the vaginal muscosa is not excised in its entirely. Rather, rectangular sections of vaginal mucosa are dissected from the anterior and posterior vaginal walls, and the denuded fibromuscular layers are sewn together to close the vaginal vault. The remaining lateral tracts of vaginal epithelium create drainage tunnels on either side of the closed vagina.

This operation may be performed quickly with general, regional, or local anesthesia. Blood loss is minimal, and success rates are high. The procedure is indicated only in elderly women who have no future desire for sexual intercourse. Because of the high incidence of stress urinary incontinence (SUI) following Lefort partial colpocleisis, concurrent anti-incontinence surgery should be considered. Additionally, high perineorrhaphy is recommended to decrease the risk of recurrent prolapse.

FIGURE 42-23.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Prolapse correction following placement of serial sutures.

Preoperative

PATIENT EVALUATION

Because access to the cervix and endometrial cavity is not possible following this procedure, preinvasive lesions should be excluded. Accordingly, a normal Pap smear should be documented prior to surgery, and evaluation of the endometrium with either endometrial biopsy or sonography is recommended.

Prolapse of the anterior, posterior, and apical compartments should be documented prior to surgery (see Chap. 24, Visual Descriptors). Additionally, urodynamic testing is performed prior to surgery to evaluate for potential SUI (see Chap. 23, Diagnostic Testing). Even without documented SUI, an adjunctive anti-incontinence procedure should be considered to prevent postoperative incontinence. Additionally, in patients undergoing Lefort partial colpocleisis who have large, global prolapse, intravenous pyelography or cystoscopy is warranted to assess for ureteral obstruction preoperatively.

CONSENT

Women considering this procedure must be fully aware that future vaginal intercourse will not be possible. Therefore, the decision to undergo this procedure should include a woman's partner. Patients expressing hesitation or doubt should be excluded as candidates.

Risks of the procedure include urinary incontinence, urinary retention, ureteral obstruction, and recurrent prolapse. Additionally, in the unlikely situation that malignancy of the cervix or endometrium develops after Lefort partial colpocleisis, the diagnosis potentially may be delayed.

PATIENT PREPARATION

Bowel preparation is administered the evening prior to surgery to effectively empty and decompress the rectum (see Table 39-10). This minimizes fecal contamination of the surgical field. Antibiotic prophylaxis is administered routinely to lower rates of postoperative wound infection.

Intraoperative

Surgical Steps

1. **Anesthesia and Patient Positioning.** General or regional anesthesia is preferred, although Lefort partial colpocleisis can be performed under local anesthesia. A patient is placed in high lithotomy position, the vagina is surgically prepared, and a Foley catheter is placed. Although Lefort partial colpocleisis may be performed in women with or without a uterus, the following description outlines the steps in women without previous hysterectomy.

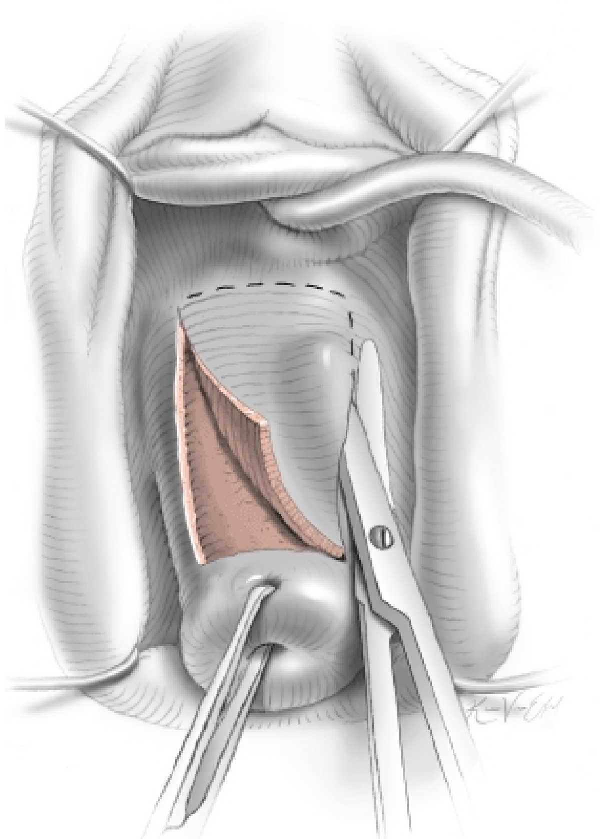
2. **Vaginal Marking.** The rectangular areas of vaginal mucosa on the anterior and posterior vaginal walls are outlined with a surgical marker or electrosurgical blade. The size of the rectangular sections to be removed is determined by the length of vaginal wall. The distal transverse incision should be placed 1 to 2 cm above the cervical os. The proximal transverse incision should lie 2 to 3 cm below the urethral meatus. The width of the incision will be determined by the size of the uterus, cervix, and vaginal walls and should be almost as wide as the prolapsed bulge. This allows multiple sutures to be placed during closure.

3. **Vaginal Infiltration.** The rectangular areas of the vaginal wall to be removed are thoroughly infiltrated with 50 mL of a dilute hemostatic solution (20 units of vasopressin in 60 mL of saline). This infiltration should extend beyond the anticipated incision boundaries. Without infiltration, significant bleeding can result from disruption of multiple small vessels during dissection.

4. **Vaginal Incision.** Previously outlined areas are incised sharply down to the fibromuscular layer.

5. **Vaginal Dissection.** A combination of sharp and blunt dissection is used to lift the mucosa away from the fibromuscular layer (Figs. 42-23.2 and 42-23.3). Dissection in the correct plane will prevent inadvertent entry into the bladder or bowel. The technique for dissection involves a finger behind the vaginal wall and dissection with Metzenbaum scissors parallel to the vaginal wall. After entry into the correct plane, blunt dissection with a sponge may allow rapid and wide development of this avascular space.

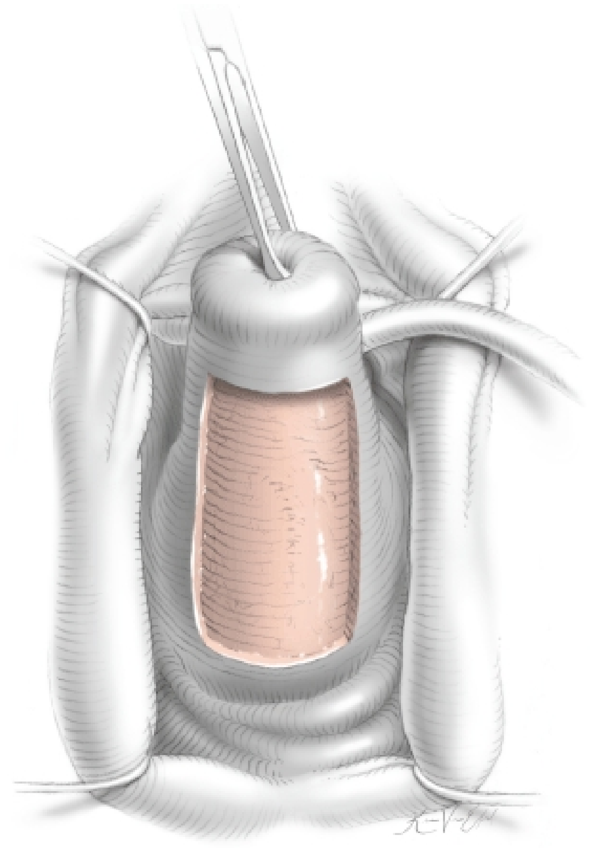
FIGURE 42-23.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Anterior vaginal wall incision.

FIGURE 42-23.3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

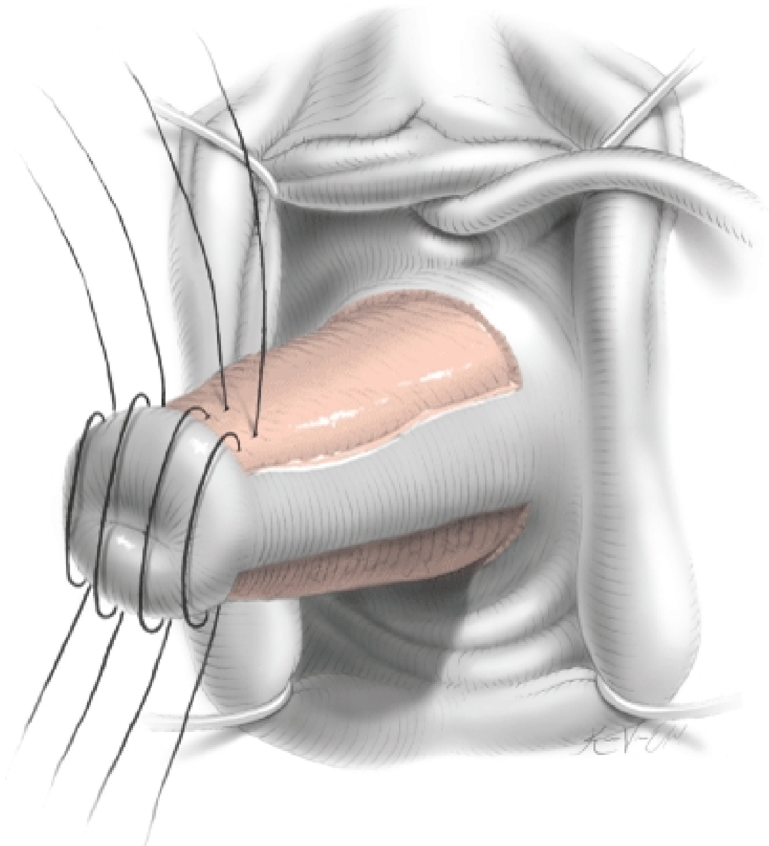
Posterior vaginal wall incision.

6. **Suture Placement.** After rectangles are removed, a row of interrupted stitches using 2-0 permanent suture is placed from the anterior to the posterior distal transverse edges (Fig. 42-23.4). These will effectively close the fibromuscular layer over the cervix.

   In creating lateral vaginal drainage canals along both the right and left sides of the incision, sutures approximate the superior and inferior edges of the rectangles. Each lateral row of sutures begins distally and progresses proximally to the original proximal transverse incision (Fig. 42-23.5).

   To elevate and replace the uterus into the pelvic cavity, the surgeon places progressively more caudad rows of interrupted sutures that approximate the anterior and posterior fibromuscular layers along the width of the incision (Fig. 42-23.6). Successive transverse tiers of sutures are placed until the proximal transverse incision is reached (Fig. 42-23.7). These rows create a tissue septum that elevates and supports the uterus (Fig. 42-23.1).

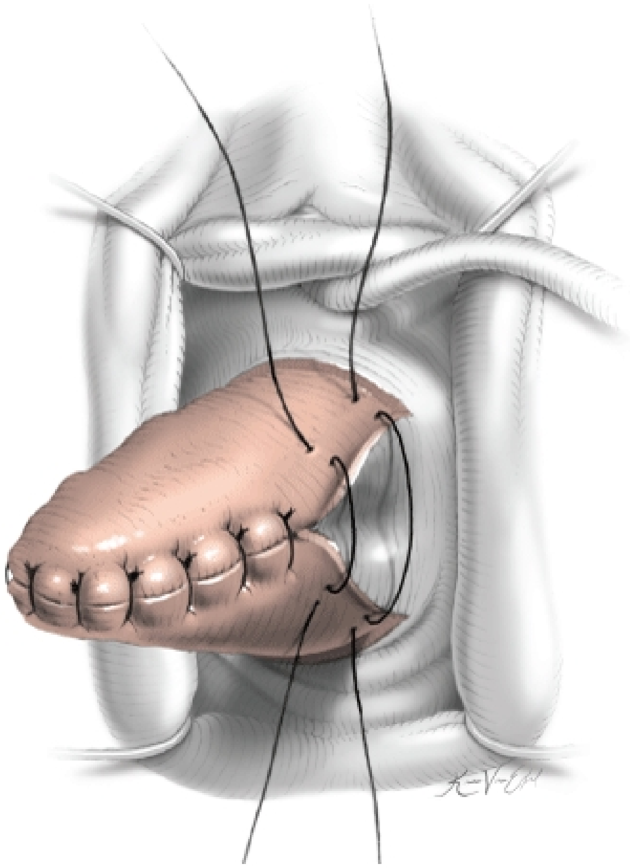
FIGURE 42-23.4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Initial suture placement.

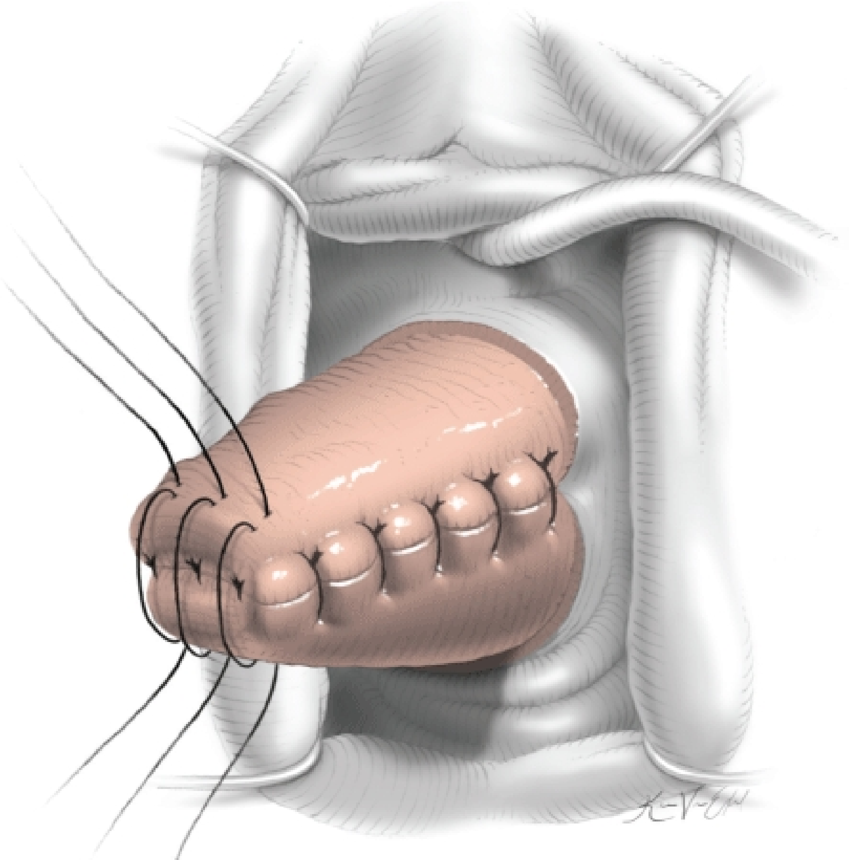
FIGURE 42-23.5



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Creation of lateral drainage canals.

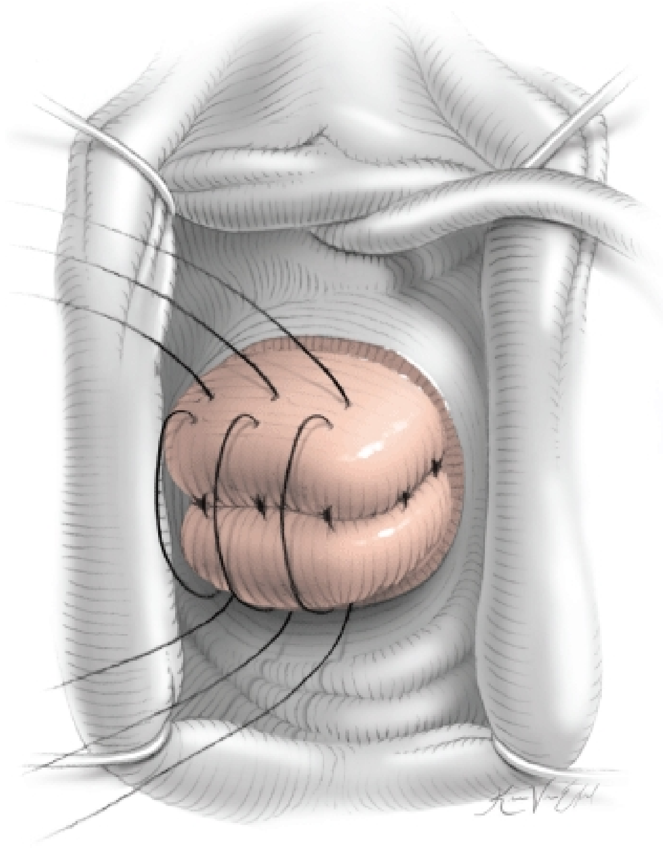
FIGURE 42-23.6



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Second row of sutures.

FIGURE 42-23.7



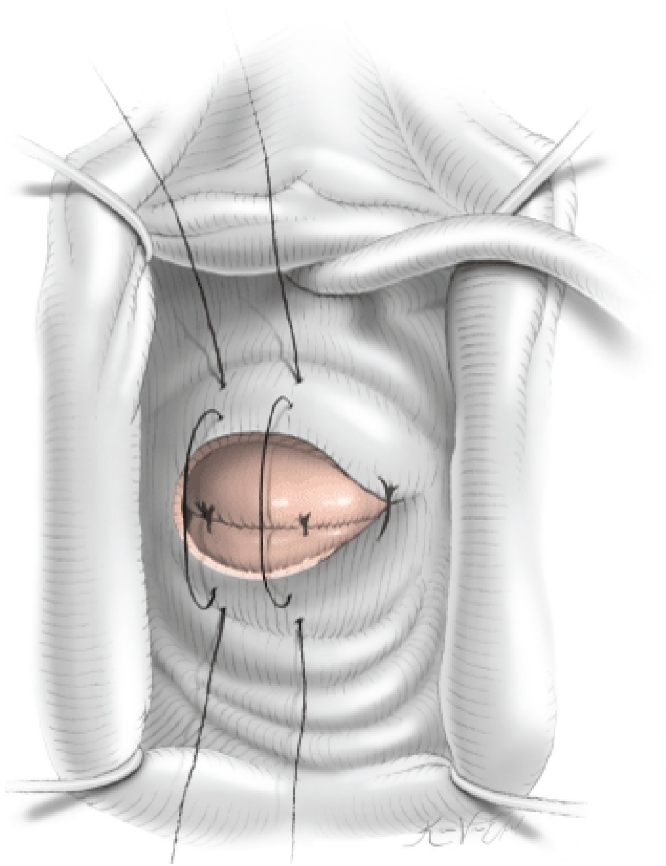
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Subsequent rows of sutures.

7. **Anti-incontinence Surgery.** At this point, an anti-incontinence procedure may be performed.

8. **Closure of the Vaginal Mucosa.** The vaginal mucosa then is closed in a running fashion with 2-0 delayed-absorbable suture, taking wide bites through the vaginal epithelium (Fig. 42-23.8).

FIGURE 42-23.8



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Vaginal mucosa closure.

9. **Perineorrhaphy.** Following closure of the vaginal mucosa, perineorrhaphy is performed as describe in Section 42-16, Perineorrhaphy.

10. **Cystoscopy.** Cystoscopy should be performed at the end of the procedure to exclude urinary tract injury and document ureteral patency (see Section 42-1, Diagnostic and Operative Cystoscopy and Urethroscopy).

Postoperative

Postoperative bladder function will depend on whether anti-incontinence surgery is performed. In general, recovery with Lefort partial colpocleisis is quick and typically without complication. Postoperative drainage should not be anticipated save for mild spotting. As with any prolapse procedure, constipation should be avoided, and administration of stool softeners is recommended. Resumption of normal activities is encouraged, with the exception of heavy lifting for several months.

42-24 COMPLETE COLPOCLEISIS

Complete colpocleisis, also termed *colpectomy,* is an obliterative procedure used for those with posthysterectomy global prolapse who do not desire future sexual activity. If the uterus is present, concurrent total vaginal hysterectomy and closure of the peritoneum are performed prior to colpocleisis.

As opposed to Lefort partial colpocleisis, with complete colpocleisis, the vaginal wall is excised in its entirety. During complete colpocleisis, the epithelial and lamina proprial layers are removed down to the fibromuscular layer (see Fig. 38-17). The operation attaches the anterior fibromuscular layer to the posterior fibromuscular layer, effectively closing the vaginal tube and replacing it back into the abdominal cavity.

The operation effectively obliterates the vagina, removing any potential for sexual intercourse. Thus the operation generally is performed in elderly women. It also may be considered in those with high surgical risks because it can be performed quickly under local or regional anesthesia and with minimal blood loss. Complete colpocleisis should be performed in conjunction with high perineorrhaphy to decrease the risk of recurrence. Consideration also should be given to performing a prophylactic anti-incontinence procedure, even in those without incontinence symptoms, because the risk of postoperative stress urinary incontinence is high.

Preoperative

PATIENT EVALUATION

This procedure is used in patients who have complete eversion of the apical, anterior, and posterior vaginal walls (see Fig. 24-8C). Women with this severe degree of prolapse often do not have stress urinary incontinence (SUI) because the urethra is kinked by prolapsing organs. However, with replacement of the prolapse, many patients do develop postoperative SUI. Therefore, urodynamic testing traditionally has been performed prior to this procedure (see Chap. 23, Diagnostic Testing). Anti-incontinence surgery is recommended for those who demonstrate latent SUI.

Frequently, women with global prolapse have some degree of ureteral obstruction. Accordingly, consideration should be given to obtaining a preoperative intravenous pyelogram (IVP) or performing cystoscopy to document ureteral patency. If ureteral patency is not confirmed, then preoperative stent placement should be considered (see Section 42-1, Diagnostic and Operative Cystoscopy and Urethroscopy).

CONSENT

Women must have absolutely no intention or desire for future intercourse. Partners should be included in the decision and consent process. Women who express any hesitancy or doubt should be excluded as candidates. Stress urinary incontinence is a definite risk with this surgery. If patients decline anti-incontinence operations, they should be aware of the significant risk of postoperative urinary incontinence.

As with any prolapse surgery, the consent process should include a discussion of the risk of prolapse recurrence, although this risk is low with complete colpocleisis. Additionally, ureteral injury also has been described with this procedure, and it should be included on consenting documents.

PATIENT PREPARATION

Bowel preparation is administered the evening prior to surgery to effectively empty and decompress the rectum (see Table 39-10). This minimizes fecal contamination of the surgical field. Antibiotic prophylaxis is administered routinely to lower rates of postoperative wound infection (see Table 39-7).

Intraoperative

Surgical Steps

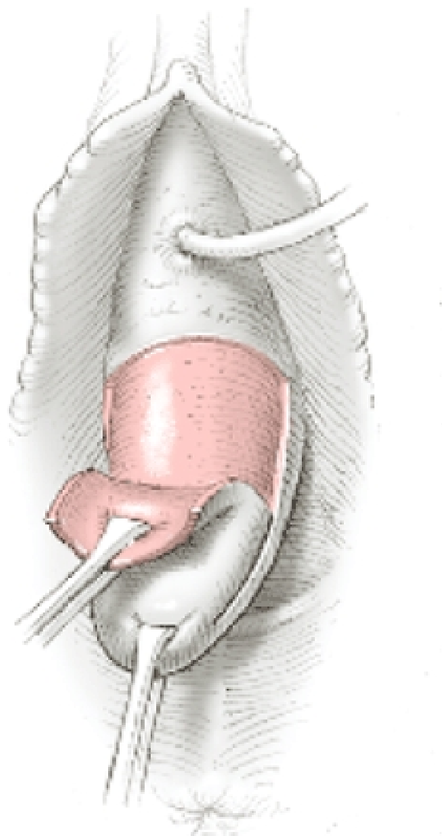
1. **Anesthesia and Patient Positioning.** General or regional anesthesia is preferred, although complete colpocleisis can be performed with local anesthesia. Following anesthesia administration, the woman is placed in high lithotomy position, the vagina is surgically prepared, and a Foley catheter is placed.

2. **Vaginal Infiltration.** Allis clamps are place laterally at 3 and 9 o'clock inside the hymenal ring and pulled to the midline without tension. This maneuver allows the surgeon to assess the amount of vaginal wall to be removed. The vaginal wall then is infiltrated thoroughly with 50 mL of a dilute hemostatic solution (20 units of vasopressin in 60 mL of saline). Without infiltration, significant blood loss can occur from disruption of multiple small vessels during dissection.

3. **Vaginal Incision.** A circumferential incision is made inside the hymenal ring around the base of the prolapsed vaginal tube. The incision should begin approximately 3 cm below the urethral meatus to allow concurrent anti-incontinence procedures.

4. **Vaginal Dissection.** A combination of sharp and blunt dissection is used to lift the vaginal epithelium and lamina propria off the fibromuscular layer (Figs. 42-24.1 and 42-24.2). Dissection in this correct plane will prevent inadvertent entry into the bladder or bowel. The technique for dissection involves positioning a finger behind the vaginal wall and dissecting with Metzenbaum scissors parallel to the vaginal wall. After entry into the correct plane, blunt dissection with a sponge may allow rapid and wide development of this avascular space. There are areas where dissection may be difficult. For example, in reaching the vaginal apex and the remnants of the uterosacral ligaments, extensive scarring may be present and requires sharp dissection. The entire vaginal epithelium is removed from the prolapsed vaginal tube.

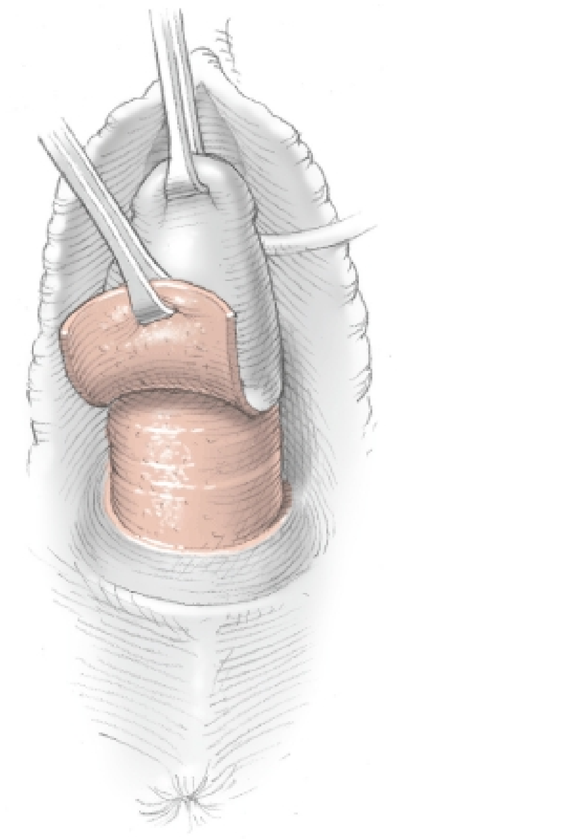
FIGURE 42-24.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Anterior vaginal wall incision.

FIGURE 42-24.2

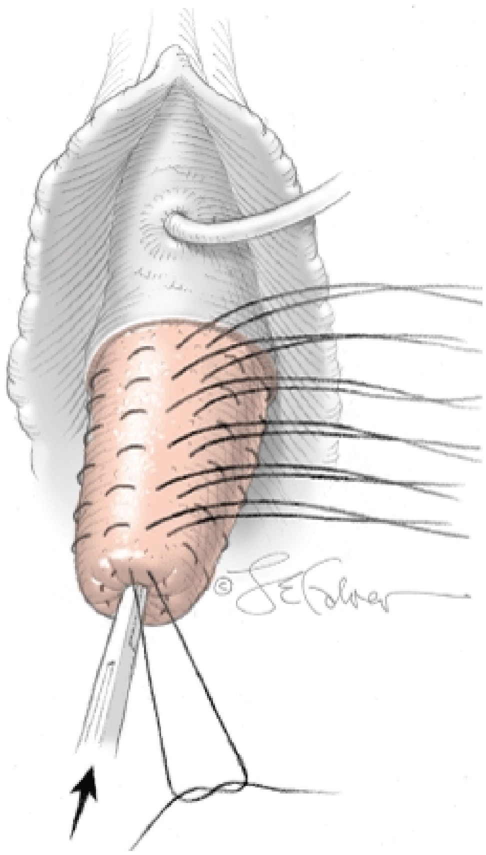


Posterior vaginal wall incision.

5. **Suture Placement.** To plicate the anterior and posterior vaginal walls together and replace the vaginal tube into the abdominal cavity, the surgeon places a series of circumferential purse-string sutures around the vaginal tube within the fibromuscular layer using 2-0 permanent suture (Fig. 42-24.3).

   The first bite is taken at 12 o'clock at the distal end of the prolapsed tube. Bites are taken circumferentially around the vaginal tube, and the knot is secured at 12 o'clock. A hemostat is placed 1 cm above the knot, and the suture ends are cut. The next circumferential suture then is place 1 cm proximal to the first suture. Prior to securing the knot on this second suture, the surgeon presses the hemostat into the apex of the vaginal tube, telescoping the tube cephalad, toward the abdominal cavity (Fig. 42-24.4A). The knot then is secured over the hemostat, effectively reducing this section of prolapsed vaginal tube. The hemostat then is removed and placed on the second suture, and the process is repeated. Depending on the size of the prolapse, approximately six to eight sutures are needed to completely invert the prolapsed vaginal tube (Fig. 42-24.4B).

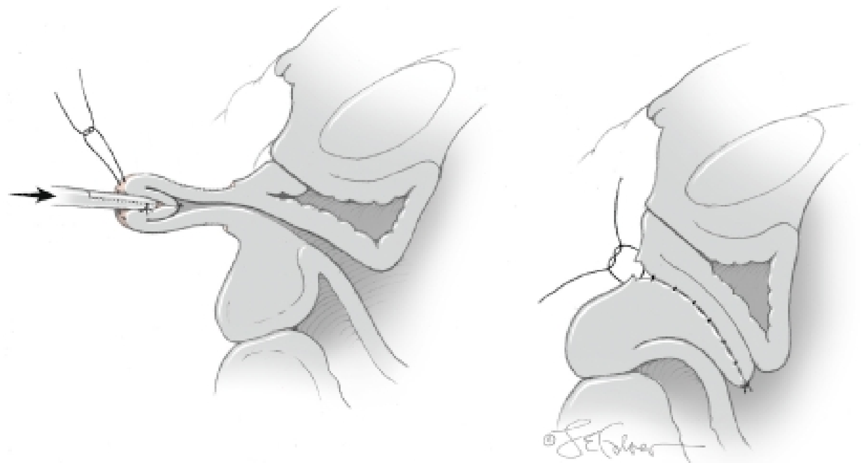
FIGURE 42-24.3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Circumferential suturing.

FIGURE 42-24.4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

A. Cephalad pressure against telescoping vaginal tube as serial sutures are secured. **B.** Completely inverted vaginal tube.

6. **Anti-incontinence Surgery.** At this point, an anti-incontinence procedure may be performed.

7. **Closure of Vaginal Mucosa.** The vaginal mucosa then is closed with a running technique using 2-0 delayed-absorbable suture, taking wide bites through the vaginal epithelium. The completed incision lies approximately 2 to 3 cm above the hymenal ring.

8. **Perineorrhaphy.** At this point, perineorrhaphy is performed, as describe in Section 42-16, Perineorrhaphy.

9. **Cystoscopy.** Cystoscopy should be performed at the procedure's completion and ureteral patency documented.

Postoperative

Postoperative bladder function will depend on whether anti-incontinence surgery is performed. In general, recovery with colpocleisis is quick and typically without complication. Postoperative drainage should not be anticipated save for mild spotting. As with any prolapse procedure, constipation should be avoided, and administration of stool softeners is recommended. Resumption of normal activities is encouraged, with the exception of heavy lifting for several months.

42-25 ANAL SPHINCTEROPLASTY

Anal sphincteroplasty re-approximates disrupted skeletal muscle fibers of the external anal sphincter (EAS) and disrupted smooth muscle fibers of the internal anal sphincter (IAS). Re-approximation may be accomplished by directly joining the ends of disrupted fibers, termed an *end-to-end sphincteroplasty.* Alternatively, disrupted ends may be overlapped and then sutured, called an *overlapping sphincteroplasty.*

Both techniques can be used to repair a third- or fourth-degree laceration immediately following a delivery or may be used in a nonobstetric setting to treat anal incontinence. Although incontinence secondary to sphincter disruption stands as a clear indication, surgical correction also may benefit those with incontinence from other etiologies, including pudendal neuropathy.

Preoperative

PATIENT EVALUATION

Some causes of anal incontinence are more amenable to surgical correction than others. For this reason, careful preoperative

evaluation should attempt to distinguish underlying sources. Evaluation for structural gastrointestinal (GI) tract pathology typically involves colonoscopy and/or barium enema. Additionally, radiographic bowel transit studies can be used to diagnose slow transit time, which may be related to symptoms of defecatory dysfunction.

Specific to the anorectum, endoanal sonography can accurately define structural disruption of the EAS and IAS (see Chap. 25, Pudendal Nerve Terminal Motor Latency Test). Anal manometry and pudendal nerve conduction studies may identify physiologic dysfunction such as neuropathy (Martinez Hernandez, 2003).

Clinicians have attempted to improve success rates by selecting only those women who may benefit most from surgery. Investigations have evaluated patient age, preoperative anal manometry readings, and pudendal nerve motor function as possible predictors of outcome. However, research findings have been conflicting, and none of these predictors has proven to be a consistent indicator of success (Bravo Gutierrez, 2004; Buie, 2001; Gearhart, 2005; Gilliland, 1998).

CONSENT

Although a significant number of women may have improved incontinence immediately following anal sphincteroplasty, the durability of this repair is poor. For example, 3 to 5 years following repair, only about 10 percent of women are fully continent to solid and liquid stool (Halverson, 2002; Malouf, 2000). The causes of long-term deterioration in function remain uncertain, but the effects of aging, postoperative scarring, and progressing pudendal neuropathy have been suggested (Madoff, 2004). In addition, it is believed that skeletal muscle repair has poor success because resting muscle tone places incision lines on constant tension. Therefore, preoperative counseling should inform that although most individuals will improve after the procedure, continence is rarely perfect, and deterioration of continence typically progresses with time.

In addition to persistent incontinence, sphincteroplasty is associated with other surgical risks. More common serious complications include wound dehiscence and fistula formation. For example, Ha and co-workers (2001) noted wound complications in 12 percent and fistula formation in 4 percent.

PATIENT PREPARATION

Because of the high associated risk of wound complications, antibiotic prophylaxis is warrant to minimize wound infection following surgical contamination from vaginal and rectal flora. We use a combination of ciprofloxican and metronidazole to obtain broad bacterial coverage. Additionally, bowel preparation is administered the night before surgery.

Intraoperative

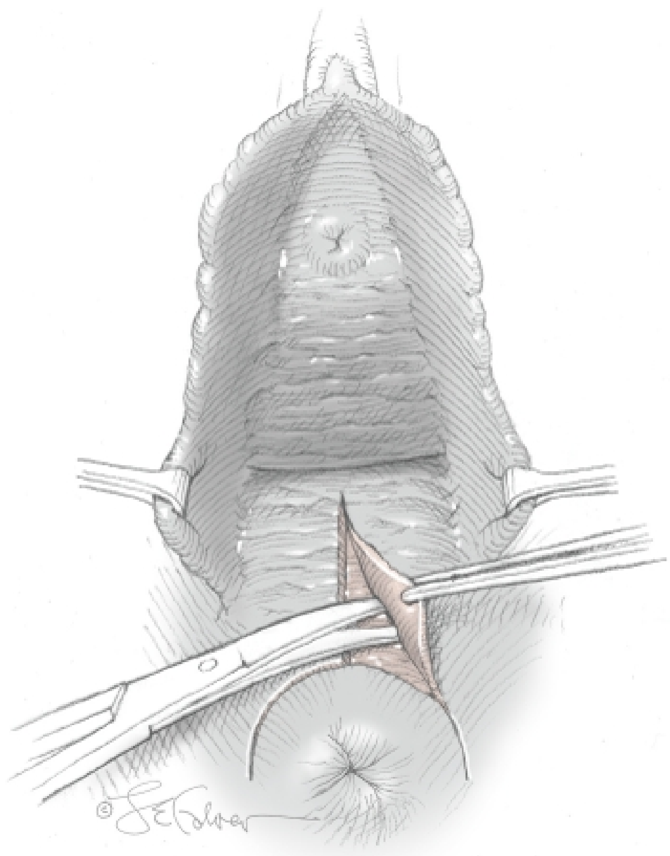
Surgical Steps

1. **Anesthesia and Patient Positioning.** After administration of either general or regional anesthesia, the patient is placed in dorsal lithotomy position, the vagina and perineum are surgically prepared, and a Foley catheter is inserted into the bladder.

2. **Incision and Dissection.** A downward arching curvilinear incision is placed between the fourchette and anus. This incision connects with a midline vaginal incision (Fig. 42-25.1). The incised edges are placed on tension with Allis clamps. Metzenbaum scissors are used to dissect disrupted ends of the EAS from surrounding and intervening scar tissue. Because of extensive scarring found frequently around these muscles, fibers may be difficult to isolate, and a nerve stimulator or a needle tip electrosurgical blade can assist in delineating these fibers. Scar tissue in the midline may be cut but should not be excised because this tissue is used in the sphincteroplasty repair to add strength to the muscle closure.

   The internal anal sphincter contributes significantly to the resting tone of the anal canal, and closure of this muscle should be included in the repair. The IAS is identified as a smooth white sheet of tissue deep to the external sphincter and superficial to the rectal wall (Fig. 42-25.2).

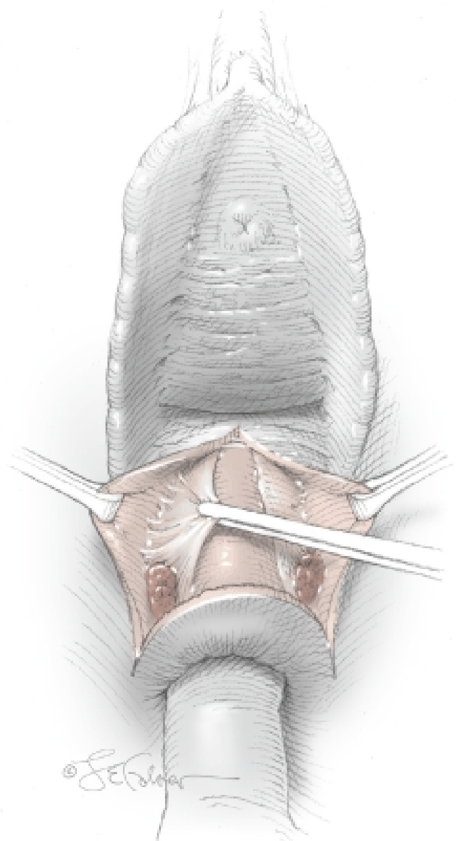
FIGURE 42-25.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Vaginal dissection.

FIGURE 42-25.2

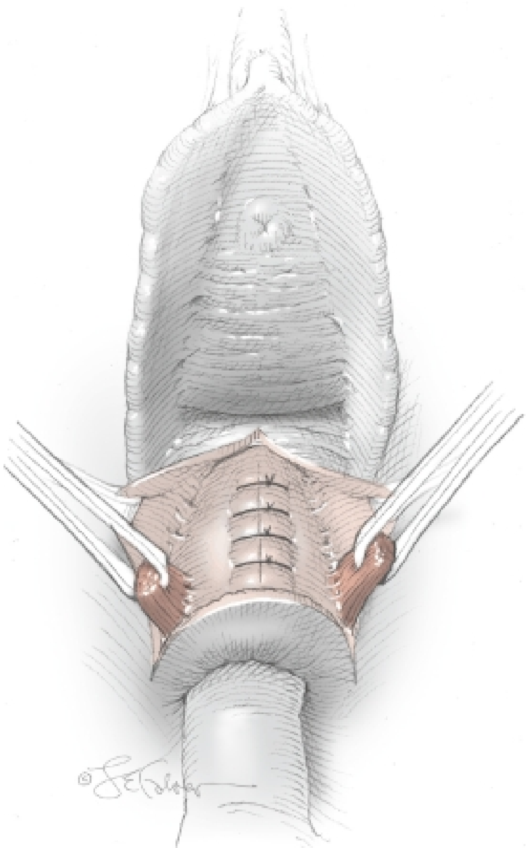


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Internal anal sphincter identification.

3. **Suture Placement within the Internal Anal Sphincter.** Interrupted stitches of 3-0 delayed-absorbable suture are used to bring the edges of the anal sphincter together in the midline (Fig. 42-25.3). Sutures are spaced approximately 0.5 cm apart, and a second row of sutures may be placed after the first is completed. Suture placement and exposure of the IAS are aided by a finger in the rectum.

FIGURE 42-25.3



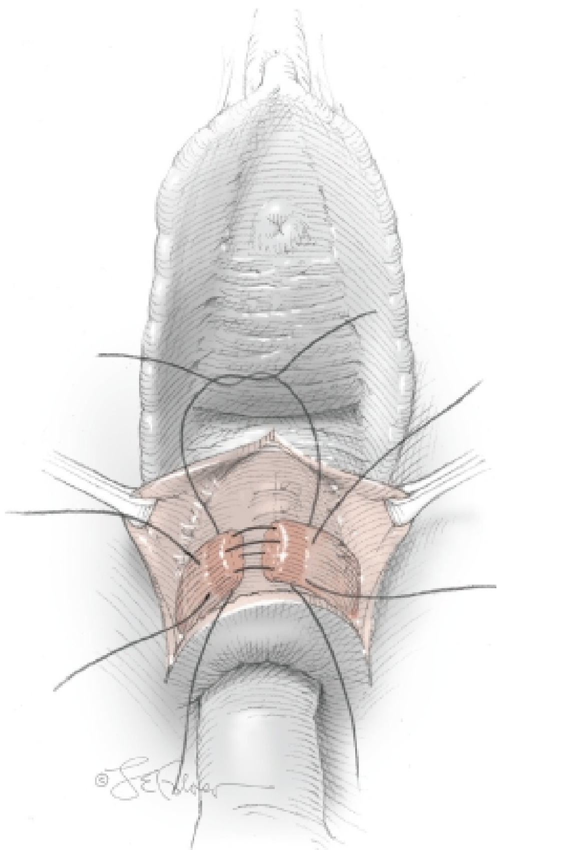
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

External anal sphincter is identified and grasped.

4. **Levator Ani Muscle Plication.** For additional support, the levator ani muscle can be plicated with interrupted stitches using 2-0 delayed-absorbable suture. This is performed after IAS closure but prior to EAS closure.

5. **Suture Placement for End-to-End External Anal Sphincteroplasty.** Each end of the disrupted EAS is identified and grasped with an Allis clamp. The ends of the EAS are brought to the midline, and a row of interrupted re-approximating stitches is placed (Fig. 42-25.4). Although many surgeons prefer the durability of permanent sutures for most pelvic reconstructive procedures, use of permanent sutures for sphincteroplasty has been associated with high rates of suture erosion and wound dehiscence (Luck, 2005). For this reason, 2-0 delayed-absorbable suture is used.

FIGURE 42-25.4

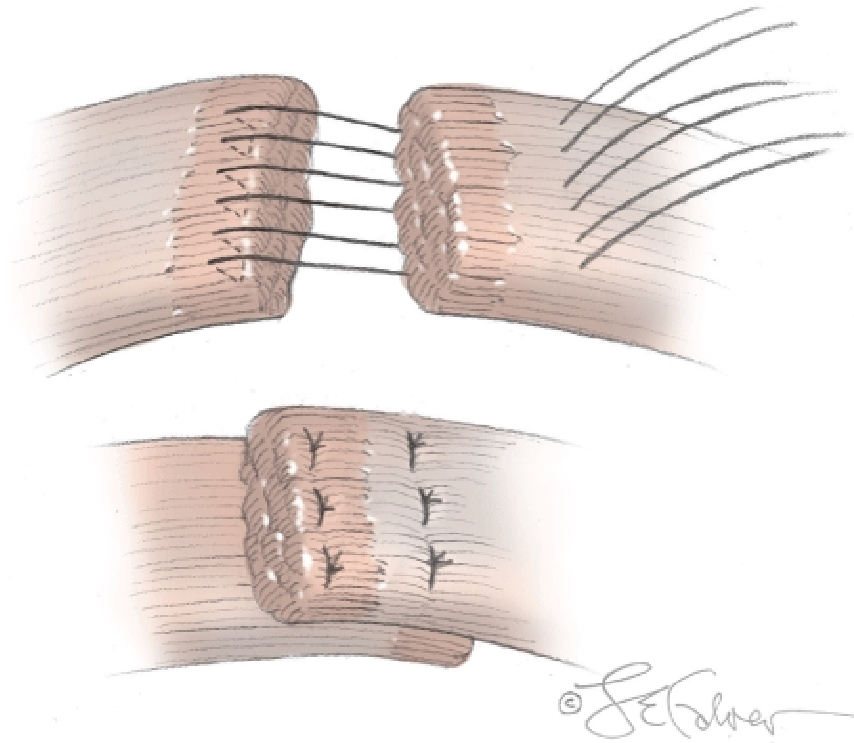


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

End-to-end sphincteroplasty.

6. **Suture Placement for Overlapping External Anal Sphincteroplasty.** With overlapping sphincteroplasty, at least 1 cm of the EAS is mobilized on each side. The ends are grasped with Allis clamps and brought to the midline, where they are overlapped. The overlapped ends are then sewn together with interrupted stitches of 2-0 delayed-absorbable suture placed in two rows, each containing two to three stitches (Fig. 42-25.5).

FIGURE 42-25.5



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Overlapping sphincteroplasty.

7. **Incision Closure.** Excision of excess perineal skin may be required prior to closing the incision. Vaginal and perineal skin then is closed in a running fashion using 2-0 delayed-absorbable suture.

Postoperative

Pain varies postoperatively, and some women can be discharged home on day 1, whereas others require longer hospitalization. The Foley catheter is removed on postoperative day 1 or 2. An active voiding trial is performed, and some women may have difficulty voiding because of pain, inflammation, and levator ani muscle spasm. To limit trauma to the healing repair, we attempt to delay defecation for several days. Patients do not eat or drink on day 1 and are subsequently advanced to clear liquids for 3 or 4 days. Stool softeners are given when a solid diet is begun and continued for at least 6 weeks. Because of the high risk of wound dehiscence and infection, oral ciprofloxacin and metronidazole are given for 10 days after the procedure. Local wound care involves sitz baths twice daily and perineal cleansing with a plastic water bottle following urination or defecation. Ambulation is encouraged, but physical exercise and sexual intercourse are delayed for 8 weeks. The first postoperative visit typically is 4 weeks following surgery.

42-26 RECTOVAGINAL FISTULA REPAIR

In general, rectovaginal fistulas that are encountered by gynecologists include those complicating fourth-degree obstetric lacerations. Less commonly, fistulas may result from gynecologic surgery or radiation therapy.

If a fistula is identified at the time or shortly after injury, then immediate repair may be undertaken. However, fistulas should not

be repaired in the setting of inflammation, induration, or infection. In addition, fistulas that are associated with radiation therapy and recurrent fistulas often require interposition of a vascular flap, such as a Martius bulbocavernosus fad pad graft, because of poor tissue vascularity (see Section 42-11, Martius Bulbocavernosus Fat Pad Flap).

Approaches to fistula repair include perineoproctotomy or transvaginal, transperineal, or transrectal techniques. The favored approach by gynecologists is the transvaginal approach and is described below. Perineoproctotomy is not recommended unless fistulas include the anal sphincter. This technique involves disruption of the anal sphincter to access the fistula and as a result, increases the risk of anal incontinence postoperatively.

Preoperative

PATIENT EVALUATION

A thorough evaluation is necessary to delineate the full extent of a fistula. If there are questions about the complexity or number of fistulas, then imaging as discussed in Chapter 26, Classification may be needed. At times, pinpoint fistulas are difficult to identify and may require examination under anesthesia with lacrimal duct probing.

CONSENT

In addition to general surgical risks, specific risks following rectovaginal fistula repair include fistula recurrence, dyspareunia, and vaginal narrowing or shortening. Fecal incontinence may follow some cases if the anal sphincter is disrupted during surgery, as with perineoproctotomy.

PATIENT PREPARATION

A rigorous bowel preparation is required to clear all stool from the rectal vault. For this reason, clear-liquid diet and an orally administered polyethylene glycol and electrolyte solution (Go-lytely, Braintree Laboratories, Braintree, MA) are advised the day prior to surgery. If stool is still present in the rectum at the beginning of surgery, then a povidone-iodine flush (Betadine, Purdue Pharma, Stamford, CT) with a Mallencot drain may be needed. Antibiotic prophylaxis is given concurrent with surgery, however, additional doses during the days before surgery are not indicated.

Intraoperative

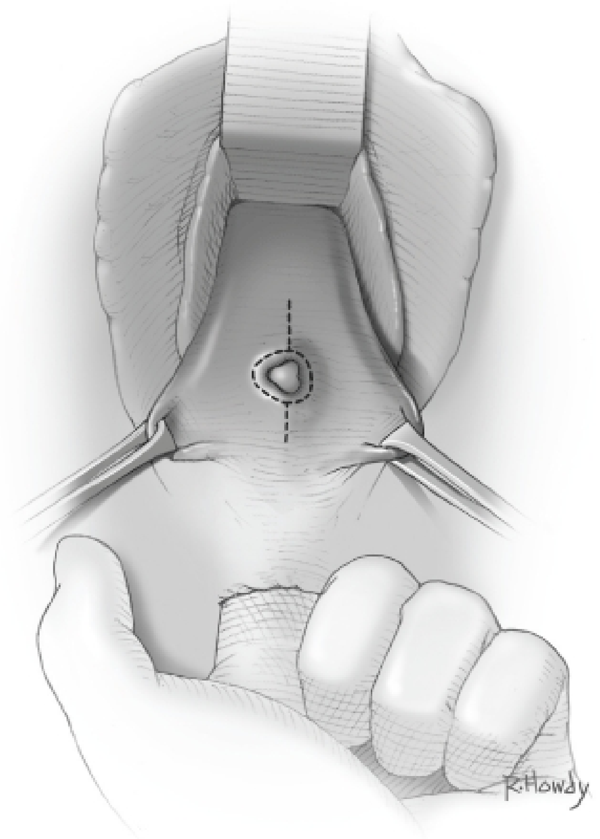
Surgical Steps

1. **Anesthesia and Patient Position.** Rectovaginal fistula repair typically is an inpatient procedure performed under general or regional anesthesia. The patient is placed in high lithotomy position with stirrups of the surgeon's choosing. The vagina is surgically prepared, and a Foley catheter is placed.

2. **Fistula Identification.** The fistula is identified, and its course is traced with the use of a probe or dilator. Moreover, small fistulas may be dilated to improve identification of the tract.

3. **Vaginal Incision.** A circular incision is made in the vaginal epithelium surrounding the fistula (Fig 42-26.1). The incision must be wide enough to allow excision of the tract and permit sufficient mobilization of surrounding tissues to close the defect without excess tissue tension (Fig. 42-26.2). The vaginal epithelium around the tract is excised sharply. The entire fistula tract then is excised (Fig. 42-26.3).

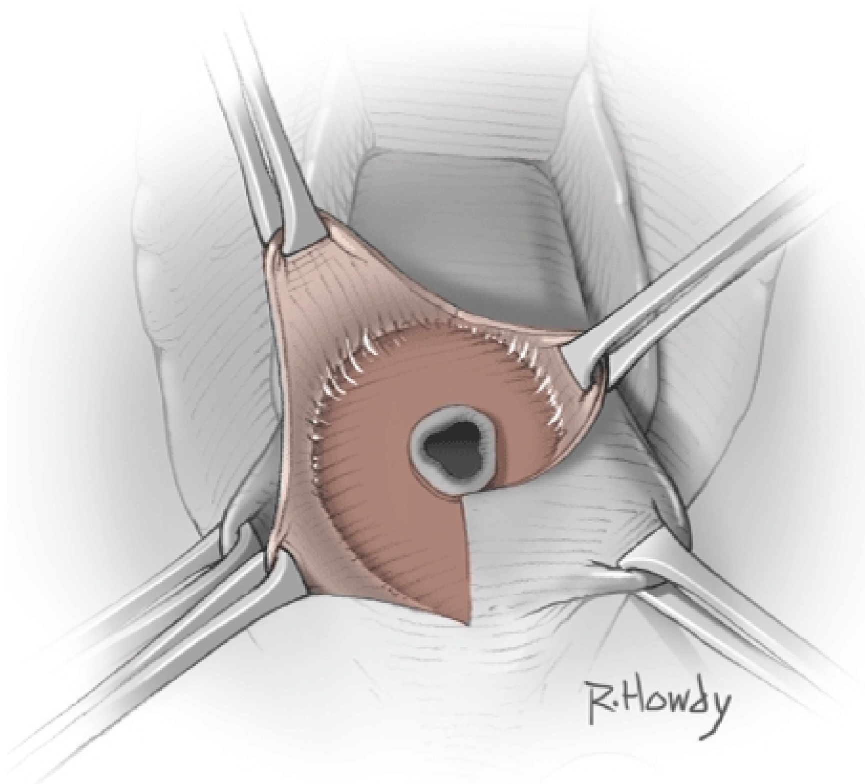
FIGURE 42-26.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Vaginal incision.

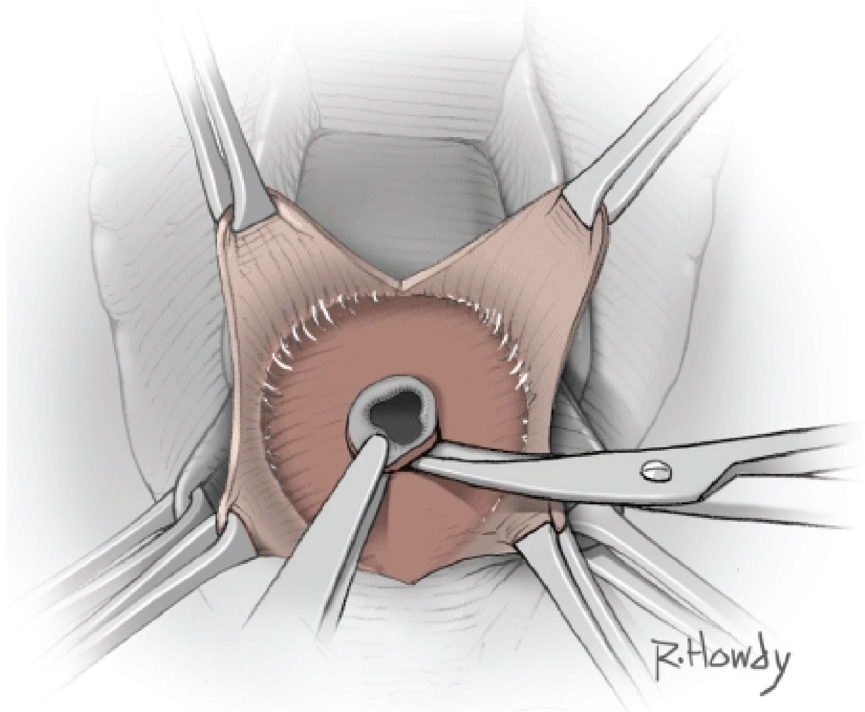
FIGURE 42-26.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Mobilization of surrounding vaginal mucosa.

FIGURE 42-26.3

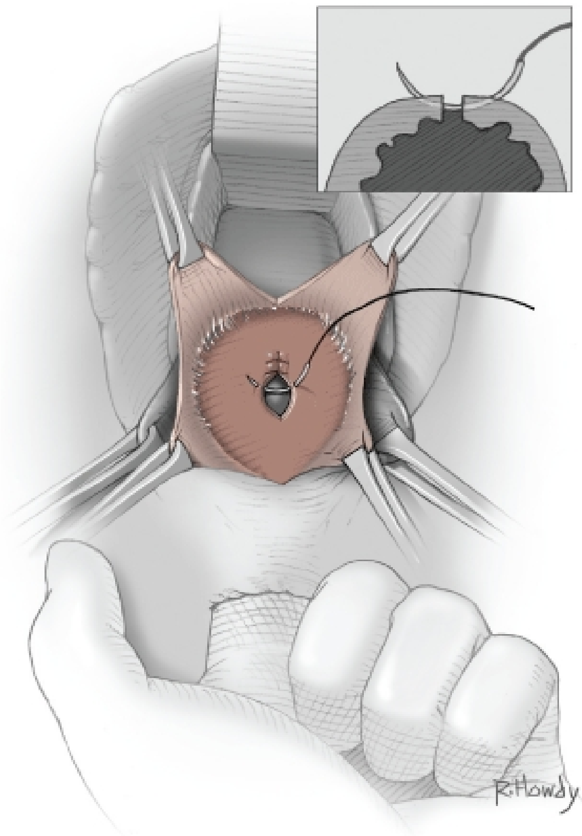


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Fistulous tract excision.

4. **Closure of the Rectal Wall.** Using 3-0 delayed-absorbable suture, a purse-string suture is placed around the defect a few millimeters from the mucosal edge. This suture is tied and inverts the defect's edges into the bowel lumen. One or two additional purse-string sutures may be placed in the rectal wall muscularis to re-inforce the closure. Alternatively, the defect may be closed with serial interrupted sutures placed within the rectal wall muscularis (Fig. 42-26.4).

FIGURE 42-26.4

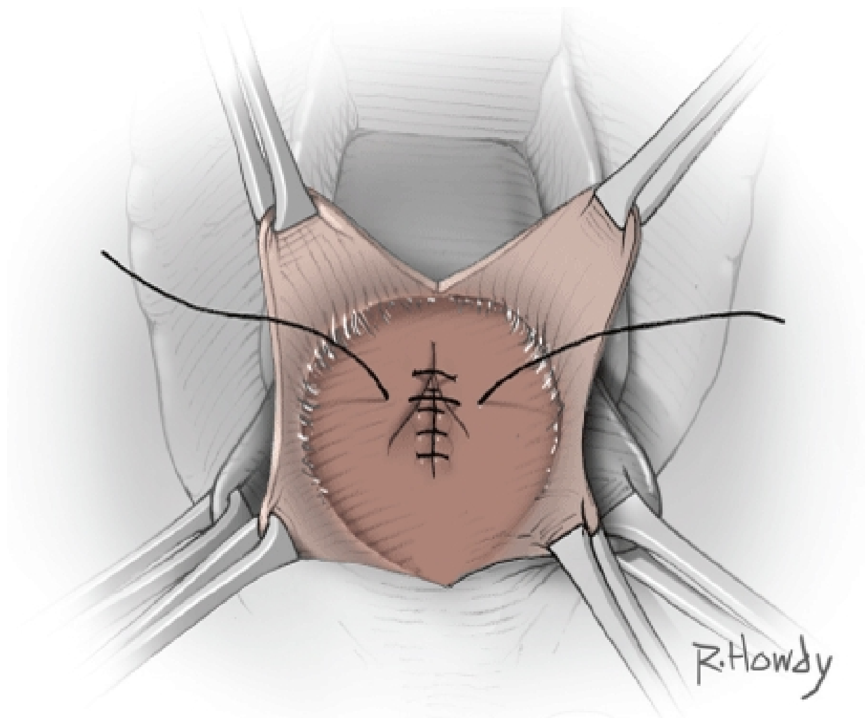


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Closure of the rectal wall.

5. **Closure of the Fibromuscular Layer.** The fibromuscular layer between the vagina and rectum is then re-approximated with interrupted stitches of 2-0 delayed-absorbable sutures (Fig. 42-26.5). If possible, two layers of closure are completed to minimize incision tension and re-inforce the repair.

FIGURE 42-26.5



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Closure of the fibromuscular layer.

6. **Martius Bulbocavernosus Fat Pad Graft.** In cases in which avascular or fibrotic tissue is extensive, a Martius graft may be placed between the fibromuscular layer and vaginal epithelium (see Section 42-11, Martius Bulbocavernosus Fat Pad Flap).

7. **Vaginal Wall Closure.** Excess vaginal mucosa is trimmed, and the vaginal mucosa is closed with a continuous running method using 3-0 absorbable or delayed-absorbable suture.

Postoperative

Normal activity can resume during the first postoperative days. Intercourse, however, should be delayed at least 1 month or until the vaginal incision is healed.

To limit trauma to the healing repair, we try to delay defecation for several days. Patients do not eat or drink on the first postoperative day and are advanced subsequently to clear liquids for 3 or 4 days. Stool softeners are given when a solid diet is begun and continued for at least 6 weeks. Constipation should be avoided. Local wound care involves sitz baths twice daily and perineal cleansing with a plastic water bottle following urination or defecation.

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43-1 RADICAL ABDOMINAL HYSTERECTOMY (TYPE III)

Radical hysterectomy differs from simple hysterectomy in that additional surrounding soft tissue is resected to achieve negative tumor margins. The operation involves wide radical excision of the parametrial and paravaginal tissues in addition to removal of pelvic lymphatics.

The five types of extended hysterectomy are discussed in Chapter 30, Radical Hysterectomy. Of these, type III (radical) hysterectomy is indicated for stage IB1 to IIA cervical cancer, for clinical stage II endometrial cancer when tumor has extended to the cervix, and for small central recurrences of cervical cancer following radiation therapy (Coleman, 1994; Cornelison, 1999).

Type III radical hysterectomy is performed most commonly abdominally. Laparoscopically assisted radical vaginal hysterectomy, however, is currently being investigated as a less invasive alternative (Hertel, 2003).

Radical hysterectomy is a dynamic operation that requires significant intraoperative decision making. Every step requires a focused, consistent surgical approach. In many ways, radical hysterectomy defines the field of gynecologic oncology, and its principles are applicable to a variety of other surgical procedures performed commonly.

Preoperative

PATIENT EVALUATION

Pelvic examination under anesthesia with cystoscopy and proctoscopy is not mandatory for all women, but clinical staging procedures should be completed. For some women with larger cervical tumors, an abdominal-pelvic computed tomographic (CT) scan may be indicated. To a lesser degree, positron-emission tomography (PET) scanning also has application in identifying metastatic disease before proceeding with radical hysterectomy (see Chap. 2, Positron Emission Tomography Imaging) (Chou, 2006).

CONSENT

Radical hysterectomy can result in significant morbidity and potentially unforeseen short- and long-term complications. These complications develop more frequently in women with obesity, prior pelvic infections, and prior abdominal surgery, which may add difficulty to performing radical hysterectomy safely (Cohn, 2000). In addition, differences in patient morbidity rates among surgeons do exist and may be of significant magnitude (Covens, 1993).

Of potential intraoperative complications, the most common is acute hemorrhage. Blood loss averages 500 to 1,000 mL, and transfusion rates are variable but high (Lentz, 1998; Rutledge, 2004). Preoperative autologous blood donation and intraoperative red cell salvage are both feasible, but their use differs significantly among surgeons (see Chap. 40, Preoperative Autologous Donation). Overall, neither strategy is consistently used (Covens, 1997; Mirhashemi, 1999).

Subacute postoperative complications may include ureterovaginal or vesicovaginal fistula (1 to 2 percent), lymphocyst formation (5 percent), and significant postoperative bladder or bowel dysfunction (20 percent) (Averette, 1993; Fotiou, 1994; Jackson, 2006). Additionally, long-term effects on sexual function, loss of fertility, and other body functions should be reviewed candidly (Bergmark, 1999).

The tone of the consenting process should reflect the extent of the operation required to hopefully cure or at least begin treatment of the malignancy. Importantly, a patient must be advised that the procedure may be aborted if metastatic disease or pelvic tumor extension is found (Leath, 2004).

PATIENT PREPARATION

A blood sample should be typed and crossed for potential transfusion. Pneumatic compression devices or subcutaneous heparin or both are particularly important because of the long anticipated length of surgery and long postoperative recovery (see Chap. 39, Prophylaxis Options) (Martino, 2006).

Bowel preparation with a polyethylene glycol electrolyte solution (GoLYTELY, Braintree Laboratories, Braintree, MA) is not mandatory but may be indicated in some circumstances. Inadvertent bowel injury should be rare unless extenuating circumstances are identified, such as previous bowel surgery, known adhesions, or prior pelvic infections.

Perioperative antibiotic prophylaxis with a third-generation cephalosporin such as cefoxitin is sufficient to prevent most surgical site-related infections. High-volume blood loss rapidly clears antibiotics from the operative site during radical hysterectomy compared with extrafascial hysterectomy. For this reason, one dose is given preoperatively and a second perioperatively (Bouma, 1993; Sevin, 1991).

CONCURRENT SURGERY

Early-stage cervical cancer is most likely to spread via the lymphatics, thus requiring adjunctive node removal (see Fig. 30-4). Pelvic lymphadenectomy typically is completed just before or immediately after radical hysterectomy. Para-aortic lymphadenectomy also may be indicated in some circumstances (see Sections 43-9, Pelvic Lymphadenectomy and 43-10, Para-Aortic Lymphadenectomy) (Angioli, 1999).

Since spread to the adnexa is much less common than via the lymphatics, removal should depend on a woman's age and potential for metastases (Shimada, 2006). In candidates for ovarian preservation, transposition of ovaries out of the pelvis may be considered in young women when postoperative radiation is anticipated (see Chap. 28, Ovary and Pregnancy Outcomes). However, in transposed ovaries, symptomatic periadnexal cysts are commonplace, and sustained ovarian function may not result (Buekers, 2001).

Intraoperative

Surgical Steps

1. **Anesthesia and Patient Positioning.** General anesthesia is mandatory, but epidural placement may aid effective postoperative pain control and decrease duration of postoperative ileus (Leon-Casasola, 1996). Bimanual examination always should be performed in the operating room before scrubbing to re-orient the surgeon to patient anatomy. Supine positioning is appropriate in most cases.

2. **Abdominal Entry.** A midline vertical abdominal incision is most common. It provides excellent exposure but typically prolongs hospital stays and increases postoperative pain (see Section 41-1, Midline Vertical Incision). Alternatively, a Cherney or Maylard incision offers postoperative advantages found with transverse incisions and allows access to the lateral pelvis (see Sections 41-3, Cherney Incision and 41-4, Maylard Incision). However, upper para-aortic nodes may not be accessible through these incisions. Pfannenstiel incisions offer limited exposure and should be reserved only for selected patients (see Section 41-2, Pfannenstiel Incision) (Orr, 1995).

3. **Exploration.** Following abdominal entry, a surgeon first should explore the abdomen thoroughly for obvious metastatic disease. Suspicious lymph nodes and any other lesions should be removed or biopsied. Confirmation of metastatic disease or pelvic tumor extension should prompt the surgeon to decide whether to proceed or abort an operation based on overall intraoperative findings and the clinical situation (Leath, 2004).

4. **Entering the Retroperitoneal Space.** The uterus is placed on traction with curved Kelly clamps at the cornua. The round ligament is sutured with 0-gauge delayed-absorbable suture as laterally as possible, and the tie is held on tension to aid entry into the retroperitoneal space. The round ligament is transected, and the broad ligament beneath separates into thin anterior and posterior leaves that contain loose areolar connective tissue between.

   The anterior leaf of the broad ligament is placed on traction and is dissected sharply to the vesicouterine fold. The posterior leaf of the broad ligament then is placed on traction and dissected sharply along the pelvic sidewall parallel to the

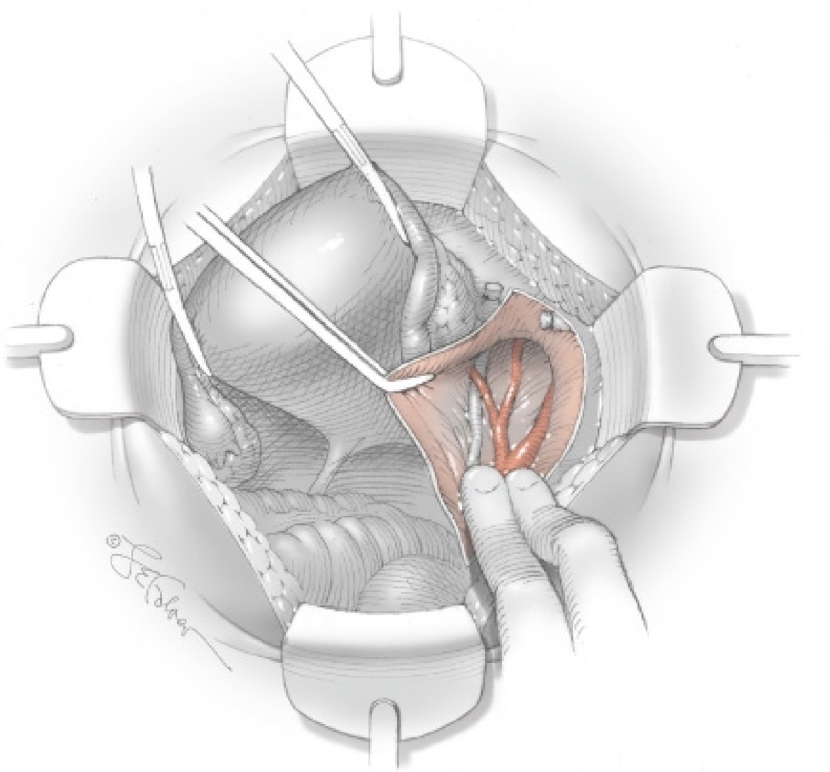
infundibulopelvic (IP) ligament.

5. **Ureter Isolation.** Loose areolar connective tissue of the lateral retroperitoneal space is dissected bluntly until the external iliac artery is palpated just medial to the psoas major muscle. The index and middle fingers then are placed on either side of the artery, and the areolar connective tissue is dissected bluntly by a "walking" motion toward the patient's head (Fig. 43-1.1).

   The medial peritoneal leaf of the broad ligament is elevated and placed on traction to permit direct identification of the common iliac artery bifurcation and origins of the external and internal iliac arteries. Blunt dissection with a finger or suction tip is used in a sweeping motion from top to bottom along the medial peritoneal leaf to identify and sufficiently mobilize the ureter, which crosses at this bifurcation.

   A Babcock clamp is used to grasp the ureter, and a Mixter right-angle clamp is used to "pop" through an underlying avascular space. A 1/4 -in-wide Penrose drain then is pulled through this space to isolate the ureter and assist in identifying its location throughout the remainder of surgery.

FIGURE 43-1.1



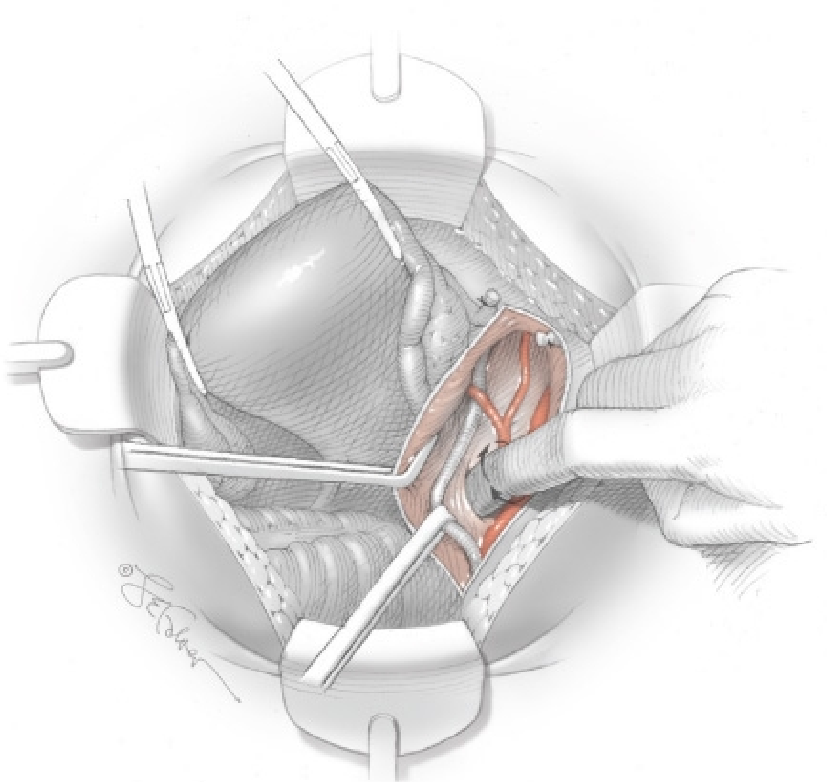
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Finding the ureter.

6. **Creating Spaces.** The pararectal space is developed by gently placing the right index finger between the internal iliac artery and the ureter and tracking in a gentle swirling motion at a 45-degree angle downward toward the midline aiming for the coccyx (Fig. 43-1.2).

Subsequently, the paravesical space is formed by holding the lateral tie of the round ligament and bluntly following the external iliac artery to the pelvic bone. The index, middle, and ring fingers of the right hand then are swept horizontally toward the midline.

FIGURE 43-1.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Making the pararectal space.

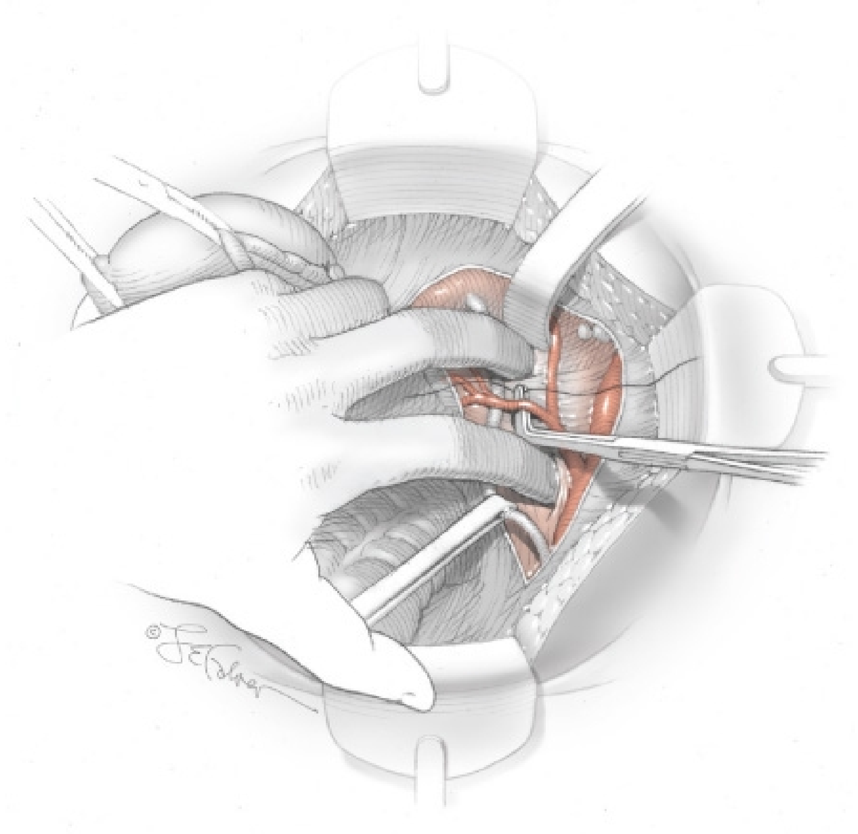
7. **Uterine Artery Ligation.** Reflection of the lateral peritoneal fold of the anterior broad ligament just distal to the round ligament should reveal the superior vesical artery (see Fig. 38-15). This vessel is dissected bluntly to better define its location and then grasped with a Babcock clamp and placed on traction. A right-angle clamp is "popped" through and beneath to create a space large enough to accommodate a narrow curved Deaver retractor. This maneuver places the superior vesical artery on traction, prevents its inadvertent ligation, and aids location of the uterine artery (Fig. 43-1.3).

   The surgeon's left hand is inserted into the pelvis with the middle finger placed in the paravesical space, the index finger in the pararectal space, and the uterus with attached Kelly clamps cupped in the palm. The uterus is held on firm traction to expose the lateral pelvic sidewall. To visualize the uterine artery, the surgeon sharply dissects parametrial attachments and intervening areolar connective tissue beginning at the internal iliac artery and continuing caudally to the superior vesical artery. The origin of the uterine artery lies between these two vessels.

   Tissues immediately proximal and distal to the uterine artery are dissected bluntly, and a right-angle clamp is placed beneath this artery to retrieve a 2-0 silk suture. The uterine artery tie is placed as close as possible to its origin from the internal iliac artery. The process is repeated to place a separate silk suture far enough medial to enable vessel transection (Fig. 43-1.3).

Silk ties help to identify the proximal and distal portions of the uterine artery throughout the remainder of the operation. A small vascular clip (Hemoclip, Weck, Research Triangle Park, NC) also can be placed lateral to the silk tie on the proximal uterine artery for additional security of hemostasis. The uterine artery then is cut. The underlying uterine vein also then may be isolated, clipped or tied, and cut.

FIGURE 43-1.3

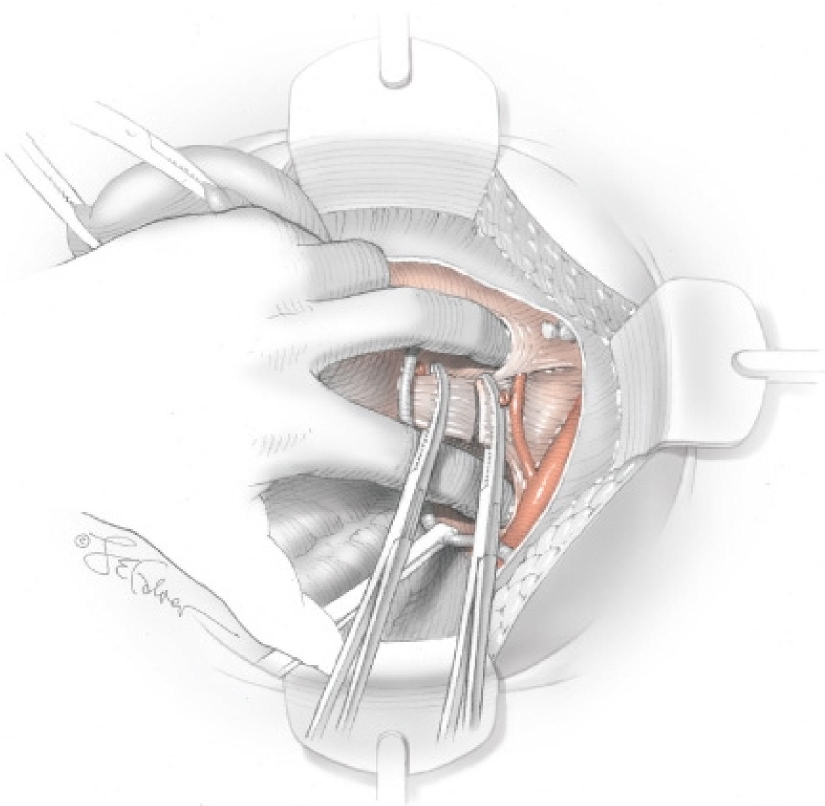


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Ligating the uterine artery.

8. **Uniting Paravesical and Pararectal Spaces.** The parametrial tissues have been pressed together by development of the paravesical and pararectal spaces. Parametrial resection to unite the spaces can be performed by several methods: (1) clamping, cutting, and suturing (Fig. 43-1.4), (2) stapling with gastrointestinal anastomosis stapler, and (3) electrosurgical blade dissection to the pelvic sidewall using a right-angle clamp to elevate and isolate parametrial tissue. Dissection is continued until the parametrium overlying the ureter is mobile.

FIGURE 43-1.4

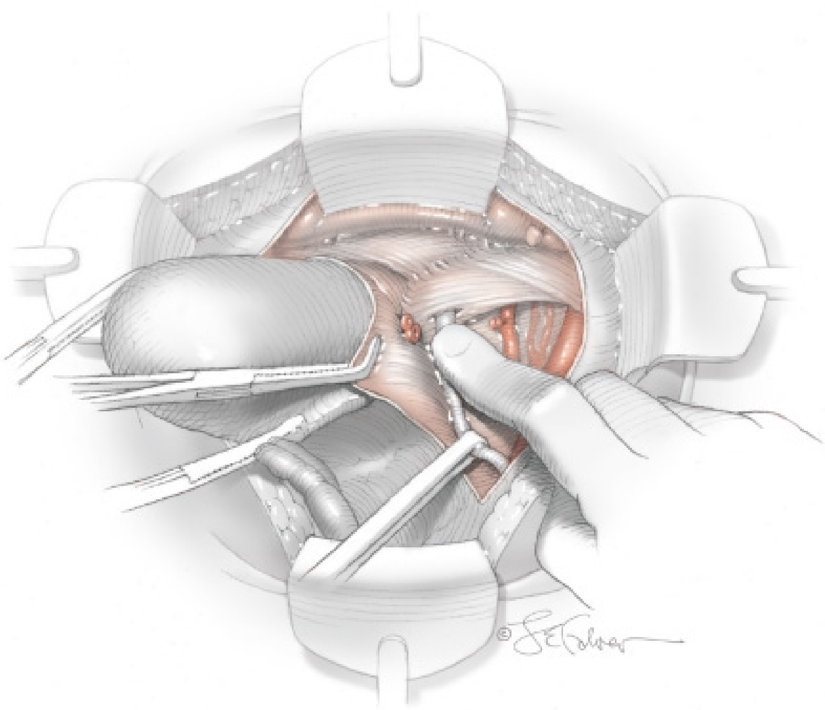


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Uniting the spaces.

9. **Ureter Mobilization.** Tips of a right-angle clamp are positioned perpendicular to and just above the ureter to detach it from the medial leaf of the peritoneum. Opening the tips parallel to the ureter creates a plane that permits it to be dissected bluntly away from the peritoneum. The ureter is placed on gentle traction by grasping the previously placed Penrose drain with the left hand. The right index finger carefully sweeps the ureter downward and laterally until a tunnel through the paracervical tissue can be palpated ventromedially as the ureter enters this tissue (Fig. 43-1.5). Additional parametrial dissection often is required to ensure that the uterine artery and surrounding soft tissue have been lifted medially over the ureter.

FIGURE 43-1.5



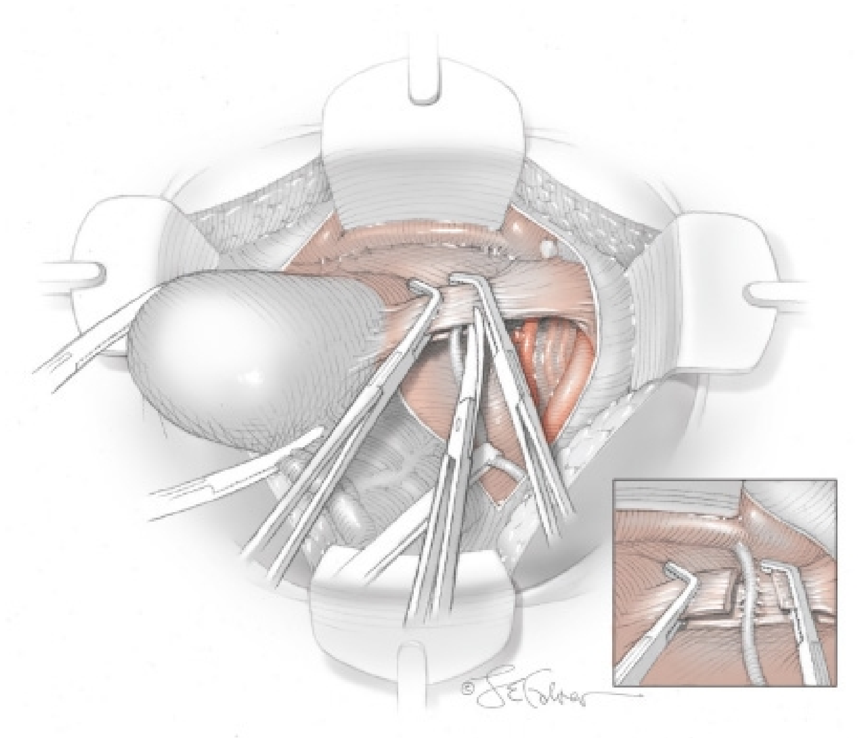
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Mobilizing the ureter.

10. **Bladder Dissection.** Electrosurgical dissection is performed to free the bladder distally from the cervix and onto the upper vagina. This may need to be repeated several times as the tunnel is progressively unroofed and the ureter is more directly visible. The bladder eventually will need to be dissected several centimeters distal to the cervical portio and onto the upper vagina.

11. **Unroofing the Ureteral Tunnel.** The uterus is placed on lateral traction, and the proximal ureter is held on traction by gently pulling on the Penrose drain. The tunnel opening should be palpated and a right-angle clamp inserted with tips directed upward while direct visualization of the underlying ureter is confirmed. The tips are directed medially toward the cervix and "popped" through the paracervical tissue. A second clamp is placed through the opening. The ureter can be dissected bluntly and pushed posteriorly toward the tunnel floor. It should be visible below before cutting the overlying paracervical tissue (Fig. 43-1.6). Delayed-absorbable 3-0 suture ties are placed for hemostasis. The same procedure may be repeated several times to completely unroof the tunnel and entirely expose the ureter. The dissection should proceed in a proximal to distal fashion with direct visualization of the ureter at all times to prevent its injury. After unroofing the ureter, it is retracted upward, and filmy attachments between the ureter and tunnel bed are sharply divided.

FIGURE 43-1.6



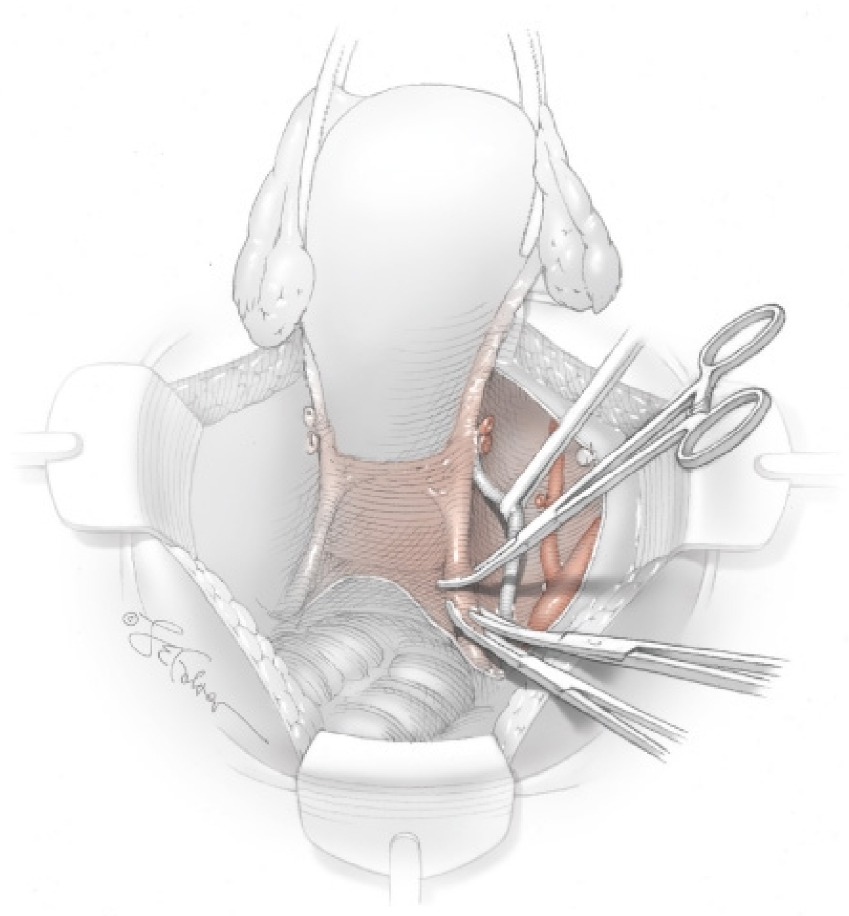
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Unroofing the ureteral tunnel.

12. **Uterosacral Resection.** Posterior radical dissection often is best performed near the operation's end because exposed retroperitoneal tissues typically ooze until the vaginal cuff is closed. The cervical external os is palpated, and an electrosurgical blade is used to superficially incise or "score" the peritoneum between the uterosacral ligaments.

    A plane is developed by gently pressing a finger toward the vaginal wall without poking through into the vault. This rectovaginal plane should be developed by gentle pressure toward the sacrum and enlarged laterally until three fingers can be inserted comfortably. This maneuver frees the rectosigmoid away from the uterosacral ligaments and prevents inadvertent bowel injury. Remaining peritoneal attachments are dissected sharply to fully expose the rectovaginal space. The exposed uterosacral ligaments can be visualized, palpated, clamped at the pelvic sidewall. They are cut and ligated with 0-gauge delayed-absorbable suture (Fig. 43-1.7). This procedure may need to be repeated to complete transection of the uterosacral ligament and adjacent supportive tissues.

FIGURE 43-1.7

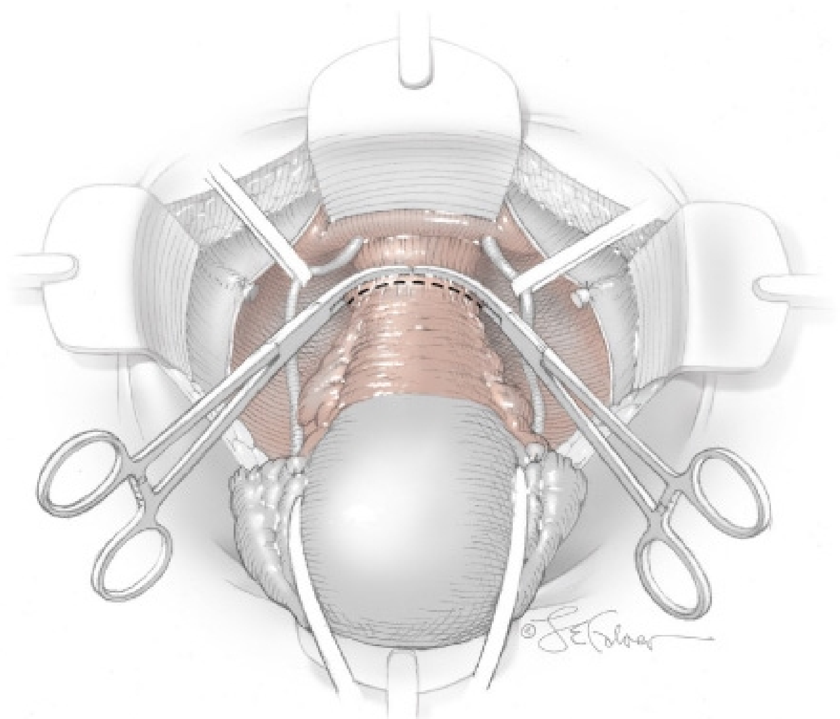


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Uterosacral resection.

13. **Vaginal Resection.** At this surgical point, a radical hysterectomy specimen should be held in place only by the paracolpium and vagina. The bladder and ureters are further bluntly and sharply dissected free until at least 3 cm of upper vagina will be included with the resected specimen. Curved clamps are placed on the lateral paracolpium with the ureter directly visible laterally. The paracolpium is cut and suture ligated with 0-gauge delayed-absorbable suture. The upper vagina then can either be: (1) clamped, cut, and suture ligated, (2) stapled, or (3) sharply transected with an electrosurgical blade and suture ligated (Fig. 43-1.8). The specimen should be examined carefully to ensure an adequate upper vaginal segment and grossly negative surgical margins.

FIGURE 43-1.8



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Vaginal resection.

14. **Suprapubic Catheter Placement** . Placement of a suprapubic catheter may aid postoperative voiding trials in carefully selected, motivated patients (Nwabineli, 1993). Through a stab incision in the lateral abdominal wall, the tip of a second Foley catheter is directed into the abdomen. The Foley catheter already within the bladder is held firmly and anteriorly in a distal extraperitoneal location. A 5-mm transverse incision is made through the mucosa of the bladder's dome using an electrosurgical blade set to a cutting mode. The Foley bulb should be directly visible, and the bladder mucosal edges are held with two Allis clamps. The second Foley catheter tip is inserted into the bladder and the balloon inflated. A snug but not tight purse-string chromic suture is placed around the bladder defect and tied. Delayed-absorbable suture in a running fashion is used to "bury" the visible Foley catheter tubing in a tunnel to its exit at the pelvic sidewall. The Foley catheter should be fixed at the skin with a permanent suture that does not occlude the tubing. The urethral Foley catheter can be discontinued postoperatively when urine is seen to be draining from the suprapubic catheter.

    Alternatively, a sole urethral Foley catheter may be placed and drainage continued until postvoid residual volumes measure below 100 mL.

15. **Ovarian Transposition.** Optionally, for those in whom preservation of ovarian function is desired, adnexa may be transposed. A distal portion of the adnexa is grasped with a Babcock clamp and placed on traction. Dissection is performed to free the IP ligament so that the adnexa can be lifted into the upper abdomen. A large vascular clip is placed on the ovary at the residual utero-ovarian ligament stump. This allows postoperative visualization of ovarian location by radiography or CT scan. Additionally, a 0-gauge silk suture is placed at this stump site and tied. Its needle is left in place.

    A hand-held abdominal retractor then is used to expose an area of the lateral posterior peritoneum as high as possible in the abdomen. The silk suture needle then is placed through the peritoneum, the adnexum is elevated by this "pulley stitch", and the suture is tied.

Dissection of the IP from the pelvic sidewall to mobilize the ovary for transposition creates a sidewall defect. The lateral pelvic defect is closed with a continuous stitch using 0-gauge delayed-absorbable suture to prevent internal herniation. The ovaries should be inspected before abdominal closure to exclude vascular compromise by transposition.

16. **Final Steps.** Active bleeding should be controlled immediately when the radical hysterectomy specimen has been removed. A dry laparotomy sponge then may be held firmly deep in the pelvis for several minutes to tamponade raw surfaces. With bleeding controlled, a surgeon should assess the vascular support to the ureter and other sidewall structures. To structures that appear particularly devascularized, an omental J-flap may provide additional blood supply (see Section 43-3, Total Pelvic Exenteration) (Fujiwara, 2003; Patsner, 1997). Routine pelvic suction drainage and closure of the peritoneum are not necessary (Franchi, 1997; Srisomboon, 2002).

Postoperative

Immediate postoperative care following radical hysterectomy in general follows that for laparotomy. Early ambulation after radical hysterectomy is especially important to prevent thromboembolic complications (Stentella, 1997). Early feeding, including rapid initiation of a clear-liquid diet, also may shorten the hospital stay (Kraus, 2000). Tenesmus, constipation, and incontinence are common immediate symptoms that should improve significantly months or years later (Butler-Manuel, 1999; Sood, 2002).

Bladder tone returns slowly, and a major cause is thought to be partial sympathetic and parasympathetic denervation during radical dissection (Chen, 2002). Thus, Foley catheter drainage commonly is continued until a patient is passing flatus because improving bowel function typically accompanies resolving bladder hypotonia. Removal of the catheter or clamping of the suprapubic tube should be followed by a successful voiding trial (see Chap. 39, Voiding Trials). A voiding trial may be attempted prior to hospital discharge or at the first postoperative visit. Patients with adequate voiding should be instructed to press gently on the suprapubic area for several days afterwards to help empty the bladder completely and prevent retention. Successful voiding may take several weeks to achieve.

Nerve-sparing radical hysterectomy is a new method demonstrating an improvement in postoperative bladder function (Raspagliesi, 2006). However, many patients have pre-existing abnormal urodynamic findings that are simply exacerbated by radical hysterectomy (Lin, 1998, 2004). In the 3 percent of women who develop long-term bladder hypotonia or atony, intermittent self-catheterization is preferred to indwelling urinary catherization (Chamberlain, 1991; Naik, 2005).

Although cervical cancer survivors treated with radical hysterectomy have much better sexual functioning than those who receive radiation therapy, more than half of surgical patients report a worse sex life postoperatively (Butler-Manuel, 1999). Severe orgasmic problems and uncomfortable intercourse due to a reduced vaginal size may develop but often resolve within 6 to 12 months. However, lack of sexual interest and lubrication may persist long-term or permanently (Jensen, 2004). Disturbances of vaginal blood flow response during sexual arousal may account for much of the reported constellation of symptoms (see Chap. 13, Arousal) (Maas, 2004). Eventually, women treated by surgery alone can expect a quality of life and overall sexual function similar to those of peers without a history of cancer (Frumovitz, 2005).

43-2 MODIFIED RADICAL ABDOMINAL HYSTERECTOMY (TYPE II)

Four procedural differences distinguish a modified radical hysterectomy (type II) from the more radical type III procedure. First, the uterine artery is transected where it crosses the ureter (instead of at its origin from the internal iliac artery). Second, only the medial half of the cardinal ligament is resected (instead of division at the sidewall). Additionally, the uterosacral ligament is divided halfway between the uterus and sacrum (instead of at the sacrum). And lastly, a smaller 2- to 3-cm margin of upper vagina is removed (instead of 3 to 4 cm). These modifications serve to reduce surgical time and associated morbidity while still enabling complete resection of smaller cervical tumors (Landoni, 2001).

Clear indications for modified radical hysterectomy are few and controversial (Rose, 2001). Stage IA2 cervical cancer is the most common presenting diagnosis (Orlandi, 1995). Type II hysterectomy is also performed on occasion for: (1) preinvasive or microinvasive disease when a more invasive lesion cannot be excluded, (2) selected stage IB1 disease with less than 2-cm lesions, and (3) small central postirradiation recurrences (Coleman, 1994; Magrina, 1999; Photopulos, 1991). In addition, a variation of

this operation may be performed when more extensive dissection is required for known benign disease (Fedele, 2005). Anatomic landmarks that distinguish a type II hysterectomy are somewhat vague and thereby allow a surgeon to sculpt the procedure to the patient's specific situation (Fedele, 2005).

Modified radical hysterectomy is performed most commonly abdominally. However, laparoscopically assisted modified radical vaginal hysterectomy is being investigated currently as a less invasive alternative (Eisenkop, 2005; Querleu, 2002).

Preoperative

Preparation for surgery should proceed with the same care and discretion that are essential for the success of radical (type III) hysterectomy (see Section 43-1, Radical Abdominal Hysterectomy (Type III)).

Intraoperative

Surgical Steps

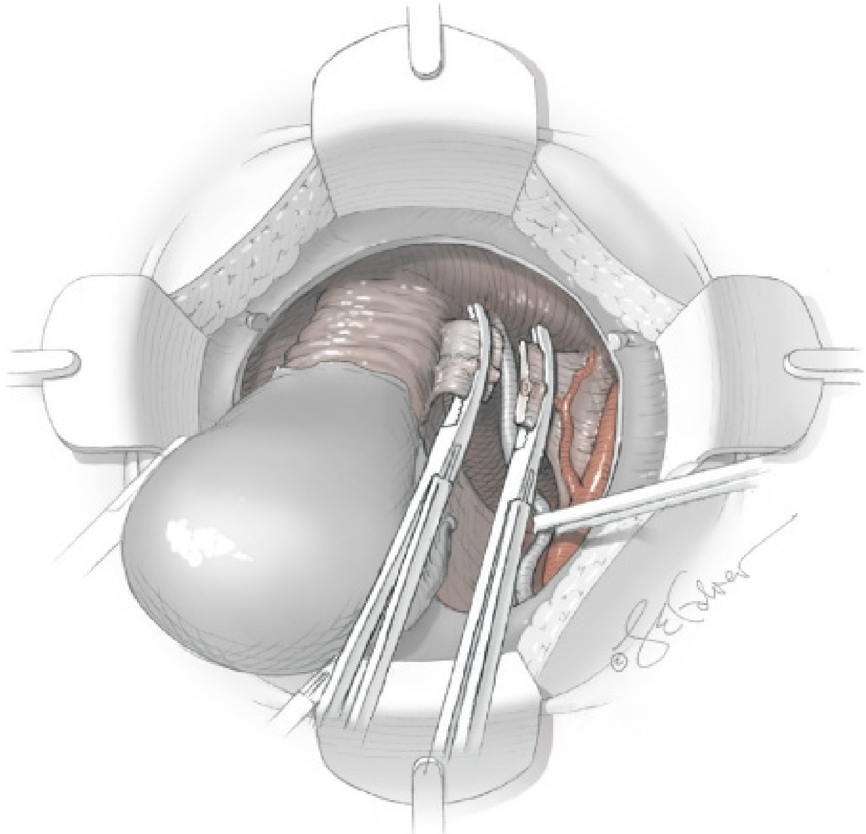
1. **Anesthesia and Patient Positioning.** Modified radical hysterectomy is performed under general anesthesia with the patient supine. Bimanual examination always should be performed in the operating room before scrubbing to re-orient the surgeon to patient anatomy. The abdomen is surgically prepared, and a Foley catheter is placed.

2. **Abdominal Entry.** Modified radical hysterectomy may be performed safely through a midline vertical or transverse incision (see Sections 41-1, Midline Vertical Incision through 41-4, Maylard Incision) (Fagotti, 2004).

3. **Retroperitoneal Dissection.** The initial steps of a modified radical (type II) hysterectomy mirror those of the type III procedure. The retroperitoneum is opened to identify structures, the ureter is mobilized, and the paravesical and pararectal spaces are developed to exclude the possibility of parametrial tumor extension before proceeding with this less radical operation (see Section 43-1, Radical Abdominal Hysterectomy (Type III)) (Scambia, 2001).

4. **Uterine Artery Ligation.** At this point, type II hysterectomy begins to differ from the radical type III procedure. The superior vesical artery does not have to be identified, nor does the entire extent of the internal iliac artery need to be dissected free of adventitial tissue. The ureteral tunnel opening should be palpated and the uterine vessels divided at that location (Fig. 43-2.1). Ligation of the uterine artery as it crosses the ureter allows preservation of distal ureteral blood supply.

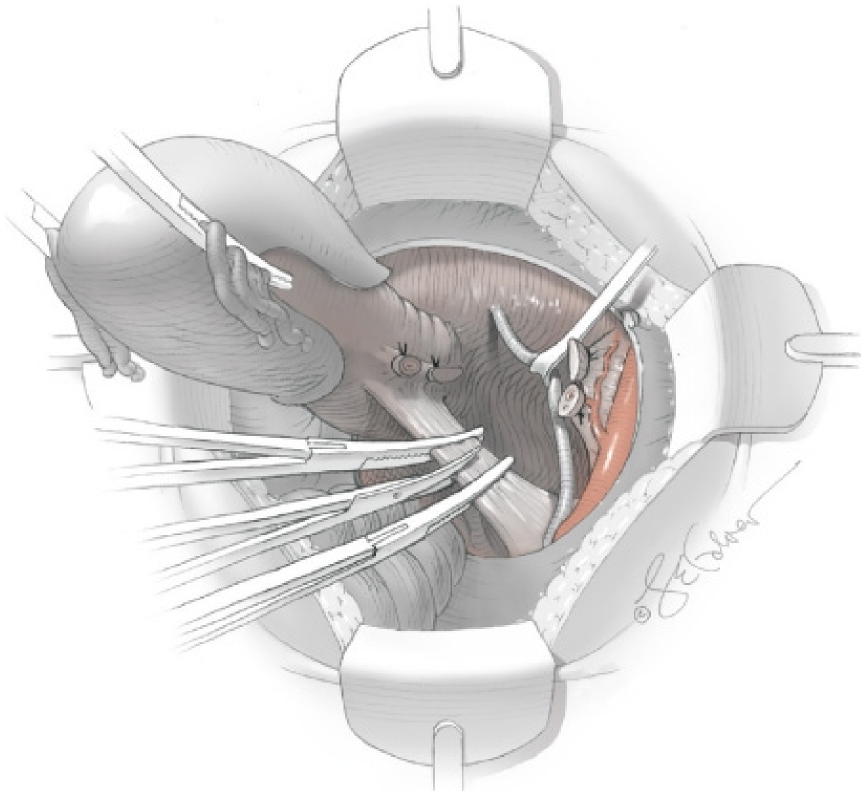
FIGURE 43-2.1



Uterine artery ligation.

5. **Cardinal Ligament Resection.** The bladder is mobilized distally off the cervix and onto the upper vagina (see Section 43-1, Radical Abdominal Hysterectomy (Type III)). Parametrial tissue at the sidewall does not have to be mobilized over the ureter in a type II hysterectomy. Posterior attachments of the ureter remain intact, and only the medial half of the cardinal ligaments are resected by successive clamping, cutting, and suture ligation of the paracervical tissue medial to the ureter. In contrast to the type III hysterectomy, the ureter is not dissected out of the tunnel bed but is rolled laterally to expose the medial cardinal ligament (Fig. 43-2.2).

FIGURE 43-2.2

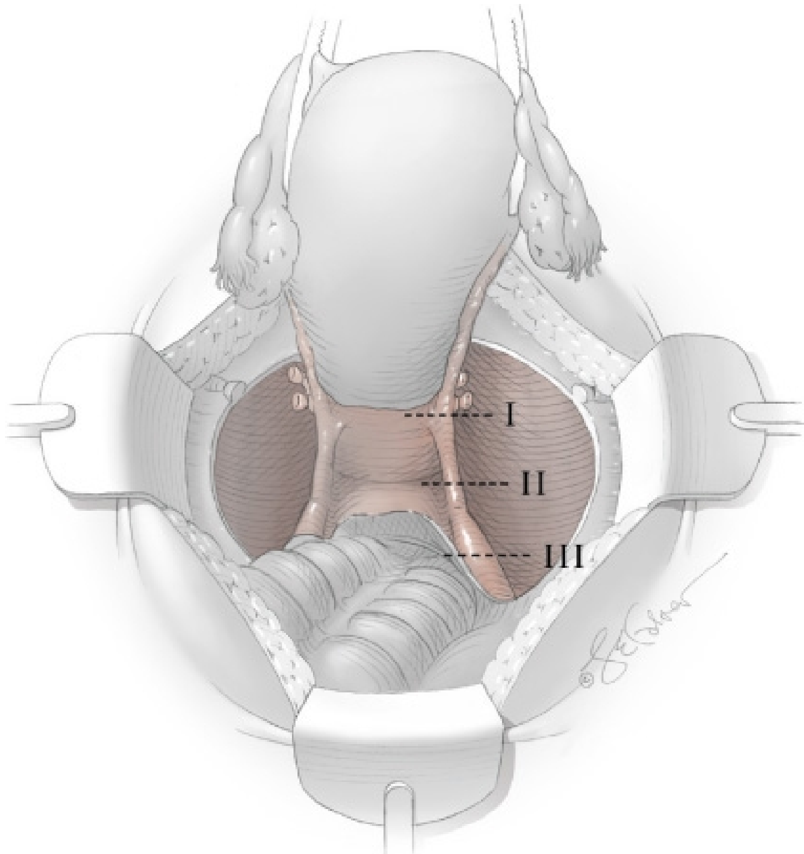


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Cardinal ligament resection.

6. **Uterosacral Resection.** Posterior dissection is also modified. Uterosacral ligaments are clamped halfway to the pelvic sidewall (instead of at the pelvic sidewall) and transected (Fig. 43-2.3). The uterus and adjacent parametrium then can be lifted well out of the pelvis, and any additional tissues also are clamped, cut, and ligated.

FIGURE 43-2.3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Uterosacral resection.

7. **Vaginal Resection.** At this point in surgery, the modified radical hysterectomy specimen should be held in place only by the paracolpium and vagina. The bladder and ureters are further bluntly and sharply dissected free until at least 2 cm of upper vagina will be included in the specimen (instead of 3 to 4 cm). Curved clamps are placed across the lateral paracolpium and vagina. Tissue directly above the clamps are cut and suture ligated. The upper vagina then can be closed with a continuous running method using 0-gauge delayed-absorbable suture. The specimen should be examined carefully to ensure an adequate upper vaginal segment and grossly negative margins.

Postoperative

In general, postoperative care follows that for radical hysterectomy but with a lower incidence of complications (Magrina, 1995). Partial sympathetic and parasympathetic denervation should be much less extensive in a modified radical hysterectomy. Thus, bladder dysfunction is much less likely than following a type III radical hysterectomy, and successful voiding occurs much earlier (Landoni, 2001; Yang, 1999). Foley catheter drainage may be discontinued on the second postoperative day and followed by a voiding trial (see Chap. 39, Voiding Trials). In addition, bowel and sexual dysfunction also should be less pronounced.

43-3 TOTAL PELVIC EXENTERATION

Removal of the bladder, rectum, uterus (if present), and surrounding tissues is the most technically challenging single procedure in

gynecologic oncology. Total pelvic exenteration is indicated most commonly for centrally persistent or recurrent cervical cancer after radiation therapy (Berek, 2005; Goldberg, 2006). Less common indications include some instances of recurrent endometrial adenocarcinoma, uterine sarcoma, or vulvar cancer; locally advanced carcinoma of the cervix, vagina, or endometrium when radiation is contraindicated, such as previous radiotherapy or malignant fistula; and melanoma of the vagina or urethra (Barakat, 1999; Geisler, 1995; Kecmanovic, 2003; Miller, 1995a; Morley, 1989).

Total pelvic exenteration generally is indicated for curative situations such as when less radical surgery, chemotherapy, or radiation options have been exhausted. However, palliative exenterations may be of benefit on rare occasions when selected patients have severe, unrelenting symptoms (Brophy, 1994; Woodhouse, 1995). Because exenteration commonly follows radiation therapy, the uterus and cervix usually lose their distinct tissue architecture and boundaries. As a result, traditional hysterectomy steps and anatomic landmark identification typically are not possible.

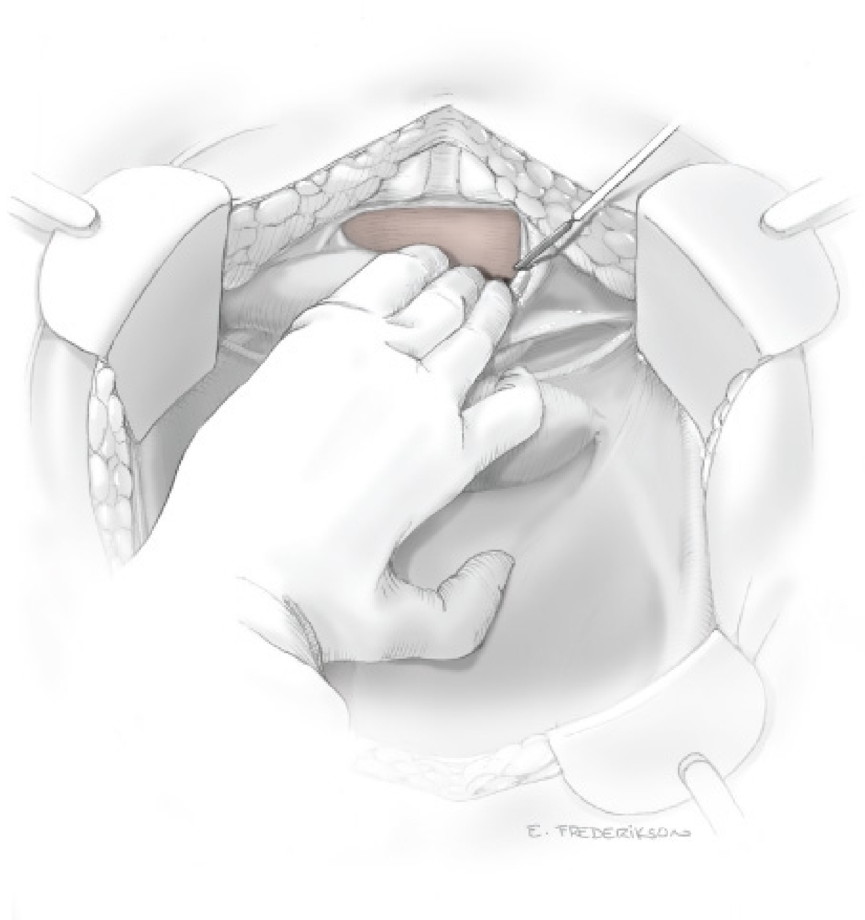
Total pelvic exenterations are subclassified based on the extent of pelvic floor muscle and vulvar resection (Table 43-3.1) (Magrina, 1997). Supralevator (type I) exenteration may be indicated when a lesion is relatively small and does not involve the lower half of the vagina. Most total pelvic exenterations will be infralevator (type II). This type is selected if vaginal contracture, prior hysterectomy, or an inability to otherwise achieve adequate margins is present. Rarely, tumor extension warrants an infralevator exenteration with vulvectomy (type III).

Table 43-3.1 Differences among Type I (Supralevator), Type II (Infralevator), and Type III (with Vulvectomy) Pelvic Exenterations

	Degree of Resection		
Pelvic Structure	**Type I**	**Type II**	**Type III**
Viscera	Above levator	Below levator	Below levator
Levator ani muscles	None	Limited	Complete
Urogenital diaphragm	None	Limited	Complete
Vulvoperineal tissues	None	None	Complete

From Magrina, 1997, with permission.

FIGURE 43-3.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Mobilizing the bladder.

Preoperative

PATIENT EVALUATION

Initially, biopsy confirmation of recurrent invasive disease should be performed. With confirmation, the single most important preoperative challenge is to search for metastatic disease that would abort plans for surgery. Chest radiography is mandatory. Abdominal-pelvic computed tomographic (CT) scanning also is indicated routinely, but a positron-emission tomographic (PET) scan may be particularly helpful (Chung, 2007). Hydroureter and hydronephrosis are not absolute contraindications unless they are due to obvious pelvic sidewall disease.

Patients often reject the entire concept of this operation initially even when faced with the knowledge that it represents their only chance for cure. Counseling is essential. Overcoming denial may take several visits. Regardless, not all eligible women will wish to proceed.

Pre-existing medical problems, morbid obesity, and malnutrition increase the potential morbidity of total pelvic exenteration. Thus, a surgeon should take all factors into consideration and candidly explore all possible alternatives before proceeding with surgical planning.

CONSENT

The consenting process is the ideal time to finalize plans for the type and location of urinary conduit, plans for colostomy or low rectal anastomoses, and need for vaginal reconstruction or other ancillary procedures. The patient also should be advised that the procedure may need to be aborted based on intraoperative findings (Miller, 1993).

For those who undergo exenteration, perioperative mortality approaches 5 percent (Dottino, 1995; Sharma, 2005). However, the mortality from progressive cancer otherwise would be 100 percent. Patients should be prepared for admission to an intensive care unit (ICU) postoperatively. Febrile morbidity, wound breakdown, bowel obstruction, and venous thromboembolic events are common short-term complications. Additionally, intestinal fistulas or anastomotic leaks or strictures may develop. Most women will experience significant morbidity and unforeseen complications (Goldberg, 2006). Re-operation may be required.

Long-term effects on sexual function and other body functions should be reviewed candidly. Patients with two ostomies have a lower quality of life and poorer body image. However, in those who retain vaginal capacity, quality of life and sexual function reportedly may be preserved. A detailed approach to the consent process can help to resolve many of these dilemmas and achieve the ideal balance for an individual patient (Hawighorst, 2004; Roos, 2004). In general, a woman's postoperative quality of life is most affected by her worries about tumor progression (Hawighorst-Knapstein, 1997). Therefore, patients should be aware that up to half will develop recurrent disease despite exenterative surgery (Goldberg, 2006; Sharma, 2005).

PATIENT PREPARATION

Patients often are admitted the day before surgery to aid important preoperative planning. Stoma sites are marked, the consent form is re-reviewed, and final questions answered.

To minimize fecal contamination during bowel excision, aggressive bowel preparation such as with a polyethylene glycol with electrolyte solution (GoLYTELY) is mandatory. Ileus is common following exenteration, and nutritional demands are increased. Thus, total parenteral nutrition may be initiated. In addition, routine antibiotic prophylaxis has been shown to decrease infectious complications (Goldberg, 1998). Pneumatic compression devices or subcutaneous heparin is particularly important owing to the anticipated length of the operation and longer duration of postoperative recovery (see Chap. 39, Prophylaxis Options). Patients should be typed and crossed for potential packed red blood cell replacement (see Chap. 40, RBC Replacement). Critical care team consultation may be indicated, and an ICU bed should be requested.

Intraoperative

INSTRUMENTS

To prepare for complicated resections, the surgeon should have access to all types and sizes of bowel staplers, which include end-to-end anastomosis (EEA), gastrointestinal anastomosis (GIA), and transverseanastomosis (TA) staplers. Additionally, a ligate-divide-staple (LDS) device may be used for vessel ligation.

Surgical Steps

1. **Anesthesia and Patient Positioning.** General anesthesia with or without epidural placement for postoperative pain management is mandatory. Invasive monitoring typically is added as a necessary precaution. Bimanual examination should be performed to re-orient the surgeon to specific patient anatomy. The abdomen, perineum, and vagina are surgically prepared, and a Foley catheter is inserted. Legs should be positioned in a low lithotomy position in Allen stirrups to permit adequate perineal access.

2. **Abdominal Entry.** The type of abdominal entry may be dictated by an intended rectus abdominis flap, but otherwise a midline vertical incision is ideal (see Section 41-1, Midline Vertical Incision). A less commonly employed option is to assess patients initially by laparoscopy. This minimally invasive approach may avoid unnecessary laparotomy in up to half of patients (Kohler, 2002; Plante, 1998).

3. **Exploration.** The most common reason that exenterations are aborted is the presence of metastatic peritoneal disease (Miller, 1993). Thus, following positioning of an abdominal self-retaining retractor, the surgeon should explore thoroughly for disseminated disease that is often not detected preoperatively. Typically, numerous adhesions also must be lysed to inspect and palpate abdominal contents. Suspicious lesions should be removed or biopsied.

4. **Lymph Node Dissection.** Approximately 40 percent of exenterations will be aborted intraoperatively due to identification of lymph node metastasis (Miller, 1993). For this reason, pelvic and para-aortic node sampling is performed to exclude metastatic disease before proceeding (see Sections 43-9, Pelvic Lymphadenectomy and 43-10, Para-Aortic Lymphadenectomy). Additionally, dissection provides a surgeon with a sense of the degree of pelvic retroperitoneal fibrosis.

5. **Pelvic Sidewall Exploration.** As described in Section 43-1, Radical Abdominal Hysterectomy (Type III) (Steps 4-6), the external iliac and internal iliac artery bifurcation is bluntly dissected free of overlying areolar connective tissue, and the ureter is placed on a Penrose drain for identification. The paravesical and pararectal spaces are developed.

   Parametrial tumor extension is the third most common reason for aborting exenteration (Miller, 1993). Thus, the pelvic sidewall should be verified to be clinically free of disease by inserting one finger into the paravesical space, another into the pararectal space, and palpating the intervening tissue down to the levator plane. There must be a grossly negative margin at the pelvic sidewall to proceed. Tissues may be biopsied and sent for frozen-section analysis to confirm this impression.

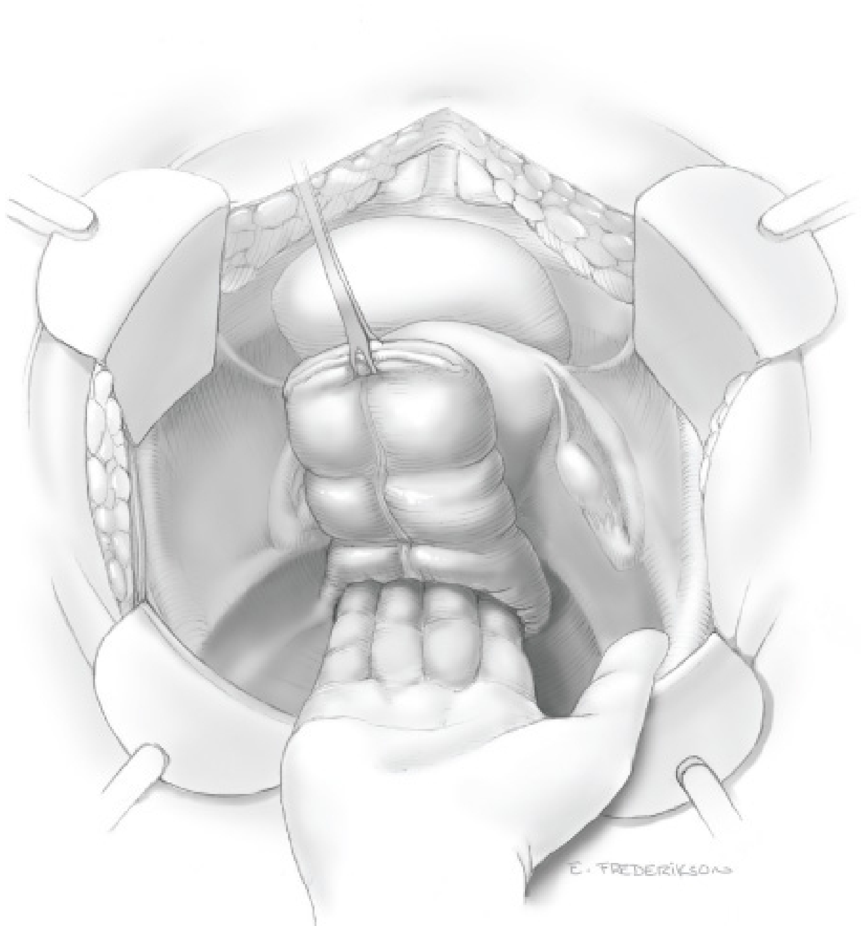
6. **Bladder Mobilization.** The bladder blade is removed from the self-retaining retractor to permit entry into the space of Retzius and blunt reflection of the bladder from the back of the pubic symphysis. Downward traction on the bladder and urethra will expose filmy attachments that may be incised electrosurgically (Fig. 43-3.1). Laterally positioned false ligaments of the bladder are divided between clamps, and this joins the retropubic and paravesical spaces. The bladder should be floppy in the pelvis from loss of its supporting pelvic attachments and completely freed anteriorly. However, the urethra is still attached to the bladder.

7. **Rectum Mobilization.** Following mobilization of the bladder, the ureters are held laterally, and the overlying peritoneum at the pelvic brim is divided in a medial direction up to the sigmoid mesentery. By inserting a finger into the pararectal space and sweeping medially, it should be possible to develop the avascular plane between the rectosigmoid and the sacrum (retrorectal space).

   Surgeons should be confident that there is no sacral tumor invasion and that they will be able to lift the rectosigmoid out of the pelvis to achieve a posterior margin that is free of tumor. This is the last decision to be made before dividing the bowel and beginning steps of the operation that are irreversible.

   Once the entire circumference of the tumor has been assessed, exenteration proceeds by dividing the sigmoid with a gastrointestinal anastomotic (GIA) stapler and dividing the intervening mesenteric tissue (see Section 43-19, Low Anterior Resection). This stapler lays two rows of staples and transects the interposed bowel. The proximal sigmoid then is packed into the upper abdomen. The distal rectosigmoid is held ventrally and cephalad while a hand is inserted posteriorly to bluntly dissect the adventitial tissue between the rectum and sacrum in the midline (Fig. 43-3.2). This maneuver is continued distally to the coccyx to develop the retrorectal space and isolate the laterally located rectal pillars.

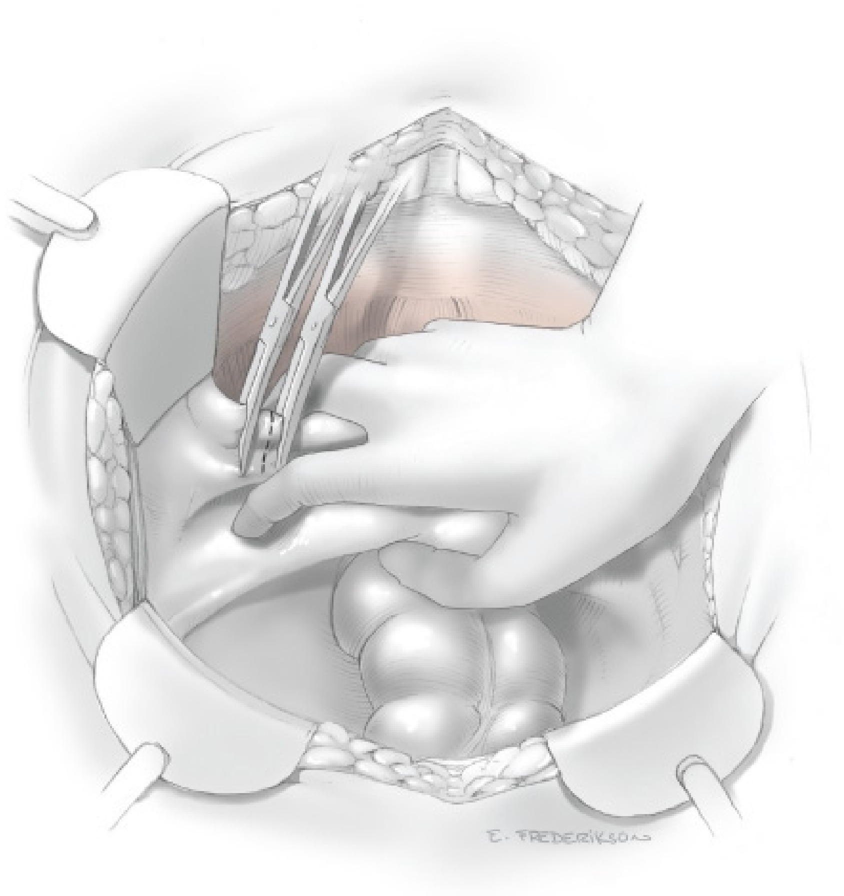
FIGURE 43-3.2



Mobilizing the rectum.

8. **Cardinal Ligaments Division.** The mobilized bladder and distal rectum with uterus (if present) are held together on contralateral traction to the incoming clamp while a hand is placed with one finger in the paravesical space and the other in the pararectal space to isolate the lateral pelvic attachments. The cardinal ligaments, internal iliac vessels, and ureter often are not distinguishable in a typically radiated field but lie within this tissue. Beginning anteriorly, these fibrous attachments are serially clamped, cut, and tied at the pelvic sidewall (Fig. 43-3.3). Vascular clips should be available in case of tissue slippage or inadvertent bleeding.

FIGURE 43-3.3

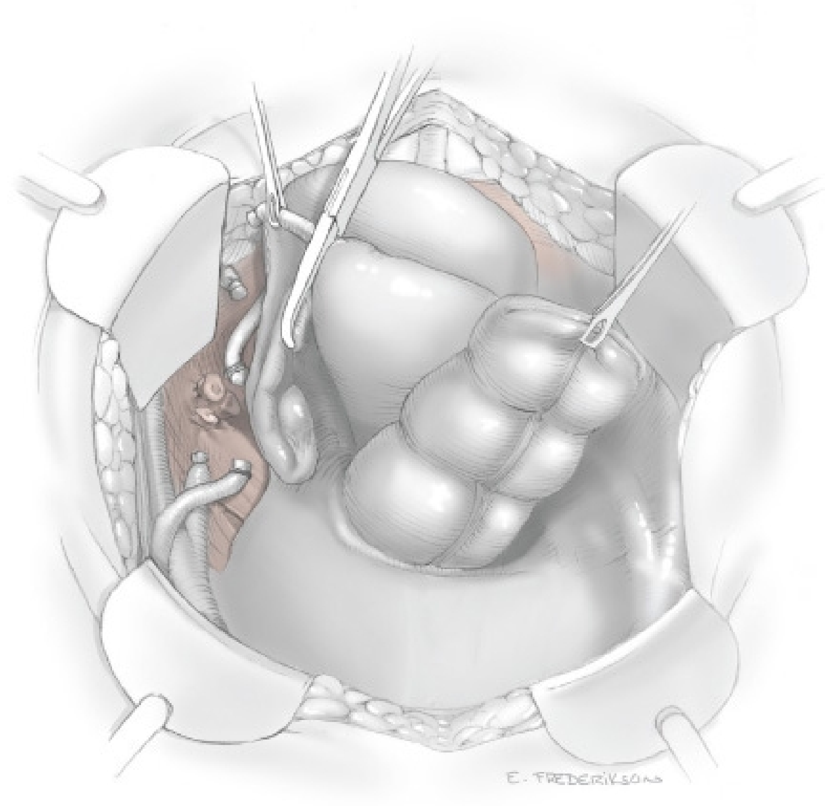


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Dividing the cardinal ligaments.

9. **Internal Iliac Vessels and Ureter Division.** As the pelvic sidewall clamping continues posteriorly along the levator muscles, the anterior branches of the internal iliac artery, venous channels, and the distal ureter ideally are individually located and ligated. However, blood vessels and ureters frequently will lie within fibrous tissue and will be relatively indistinguishable. Thus, clamps should be placed around smaller pedicles to minimize the possibility of inadvertent blood loss. At minimum, the ureter should be located, isolated, and divided. A large vascular clip is placed on its proximal end to distend the ureter and aid anastomosis into the planned conduit. Dissection then is repeated on the contralateral side, and any remaining lateral attachments along the levator ani muscles are divided as the pelvic floor curves toward the perineum (Fig. 43-3.4).

FIGURE 43-3.4

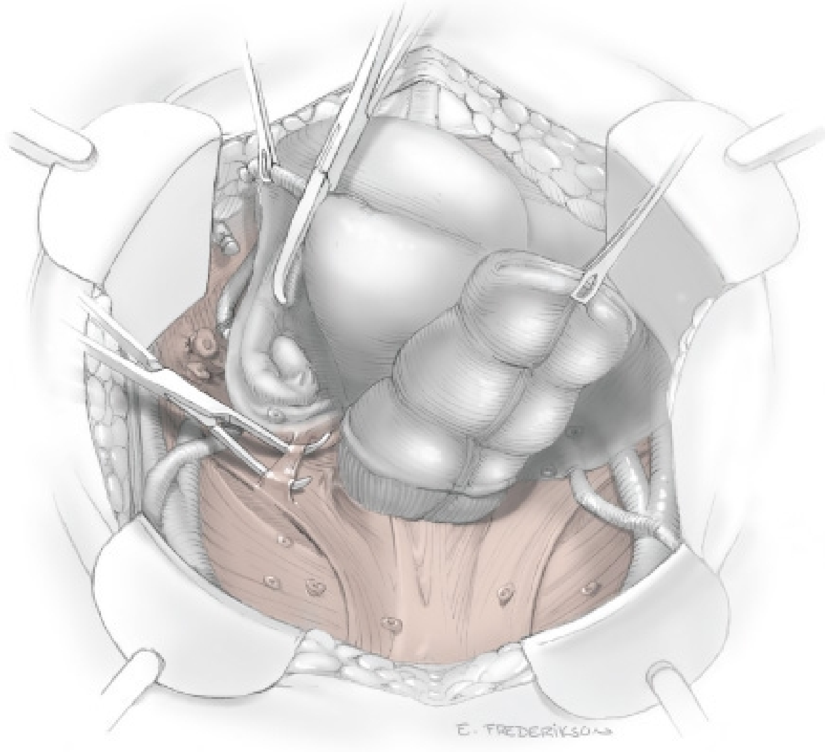


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Dividing the hypogastric vessels and ureter.

10. **Rectal Pillar Division.** The exenteration specimen now is chiefly tethered by the rectal stalks and distal mesenteric attachments posteriorly. These can be isolated with a right-angle clamp and divided along the pelvic floor (Fig. 43-3.5). This maneuver is continued distally to expose the entire posterior pelvic floor. The exenteration specimen then is inspected circumferentially, and additional dissection is performed to completely release it from all attachments leading through the levator ani muscles.

FIGURE 43-3.5

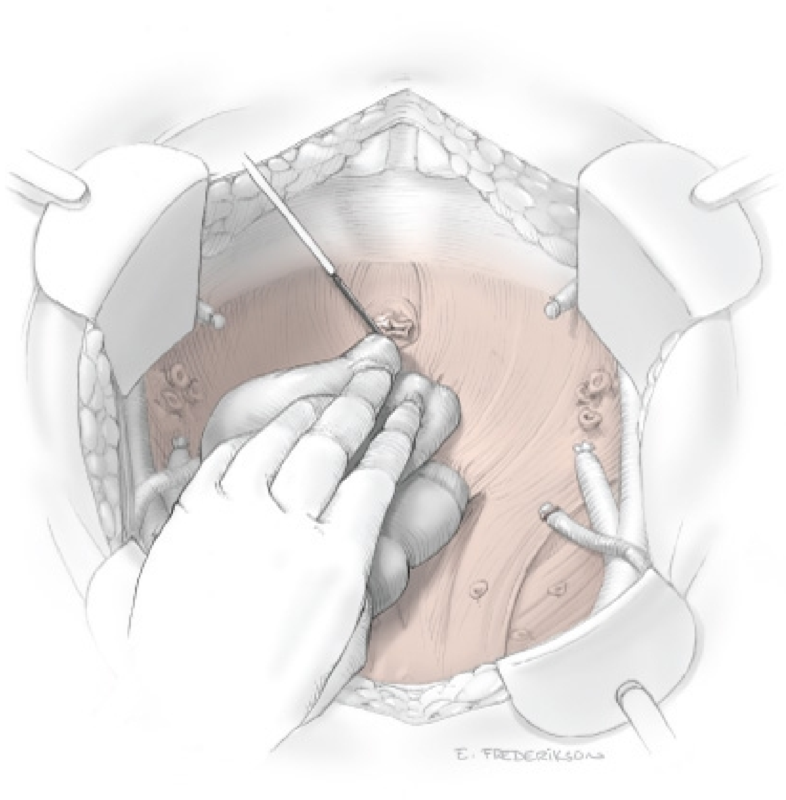


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Dividing the rectal pillars.

11. **Supralevator Exenteration: Final Steps.** Removal of the specimen above the levator muscles begins by posterior traction on the bladder. The Foley catheter should be palpable within the urethra, and all surrounding tissue already should be dissected away. An electrosurgical blade is used to transect the distal urethra (Fig. 43-3.6). The distal opening does not require closure and may act as a drain postoperatively. The vagina then is transected and closed with delayed-absorbable suture in a running fashion. The transverse anastomosis (TA) stapler is placed across the distal rectum and fired. This stapler places one row of staples but does not transected tissue following application of the staple line. Therefore, a surgeon must sharply cut above the staple line to separate proximal and distal bowel segments. This completes detachment of the specimen, which includes bladder, uterus, rectum, and surrounding tissue (Fig. 43-3.7). The pelvic floor then is assessed carefully to identify bleeding points (Fig. 43-3.8). A laparotomy pad is packed firmly into the pelvis to tamponade any surface that is oozing while the exenteration specimen is inspected to confirm grossly negative margins.

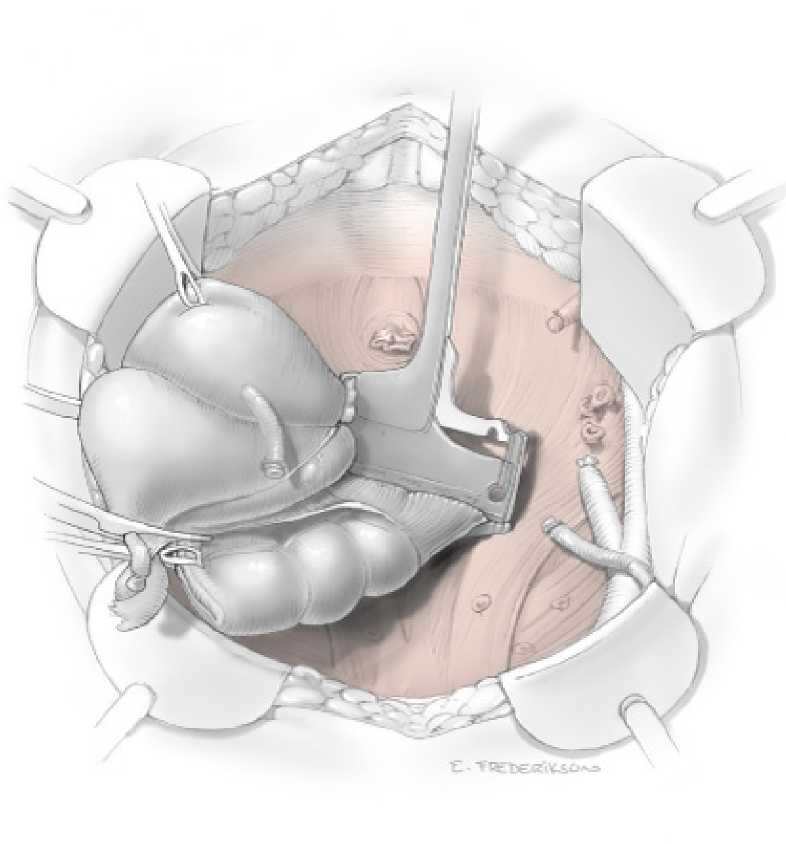
FIGURE 43-3.6



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Supralevator exenteration: dividing the urethra.

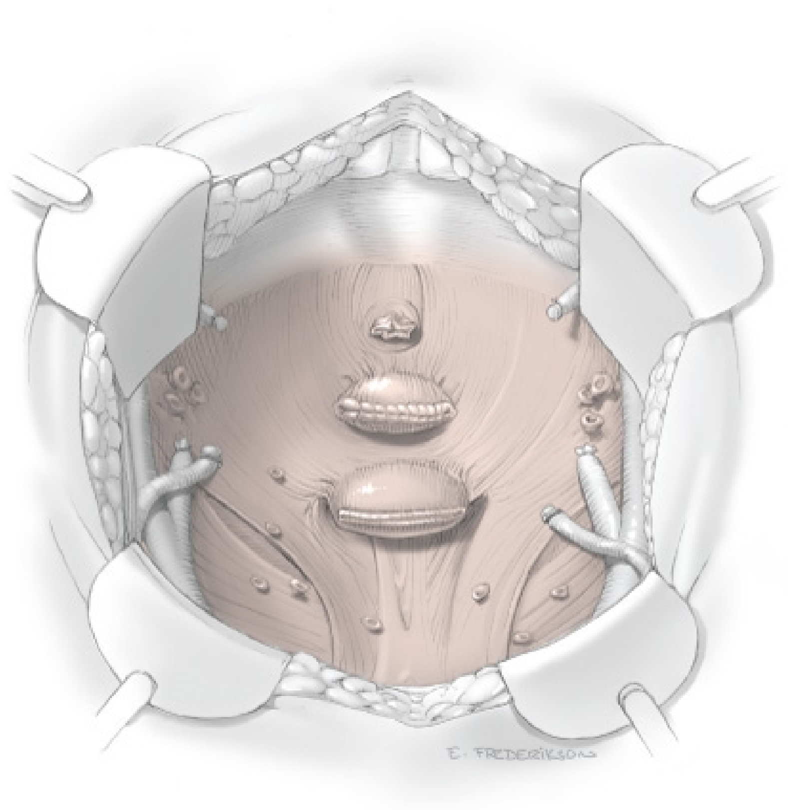
FIGURE 43-3.7



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Supralevator exenteration: dividing the rectum.

FIGURE 43-3.8



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Supralevator exenteration: appearance of the pelvic floor.

12. **Infralevator Exenteration: Perineal Phase.** When the abdominal dissection reaches the levator muscles, a second surgical team begins the perineal phase. The use of two teams typically shortens operative time and reduces bleeding. The planned perineal resection is outlined to encompass the tumor. As shown in Fig. 43-3.9, resection may require infralevator exenteration without vulvectomy or infralevator exenteration with vulvectomy.

    The perineal incision ideally begins concomitantly with division of the levator muscles by the abdominal team. An electrosurgical blade is used to dissect around the urethra, vaginal opening, and anus.

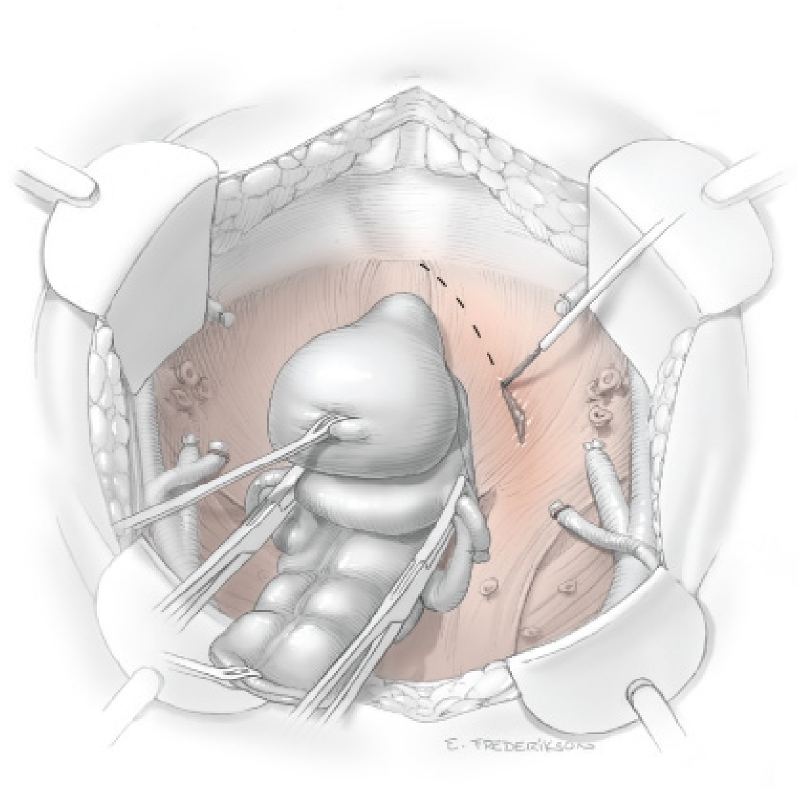
FIGURE 43-3.9

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Infralevator exenteration: perineal phase incisions.

13. **Infralevator Exenteration: Partial Resection of the Levator Muscles.** Within the abdomen, the primary surgical team places the specimen on traction. Electrosurgical blade dissection is used to incise the levator ani muscles circumferentially lateral to the area of tumor extension (Fig. 43-3.10). The dissection proceeds distally toward the perineum.

FIGURE 43-3.10



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Infralevator exenteration: partial resection of the levator muscles.

14. **Infralevator Exenteration: Connecting the Perineal and Abdominal Spaces.** After the perineal incision has reached the fascial plane, four spaces are developed: subpubic space, left and right vaginal spaces, and retrorectal space. It is helpful to have the abdominal surgeon place a hand deep into the pelvis to guide the electrosurgical dissection by the perineal team (Fig. 43-3.11). Five pedicles should be identified that separate these avascular spaces: two pubourethral, two rectal pillar, and the midline posterior anococcygeal. Electrosurgical dissection that is directed by the abdominal surgeon's finger is performed to open the spaces. From below, clamps then are placed on the intervening five vascular pedicles, which then may be divided and ligated.

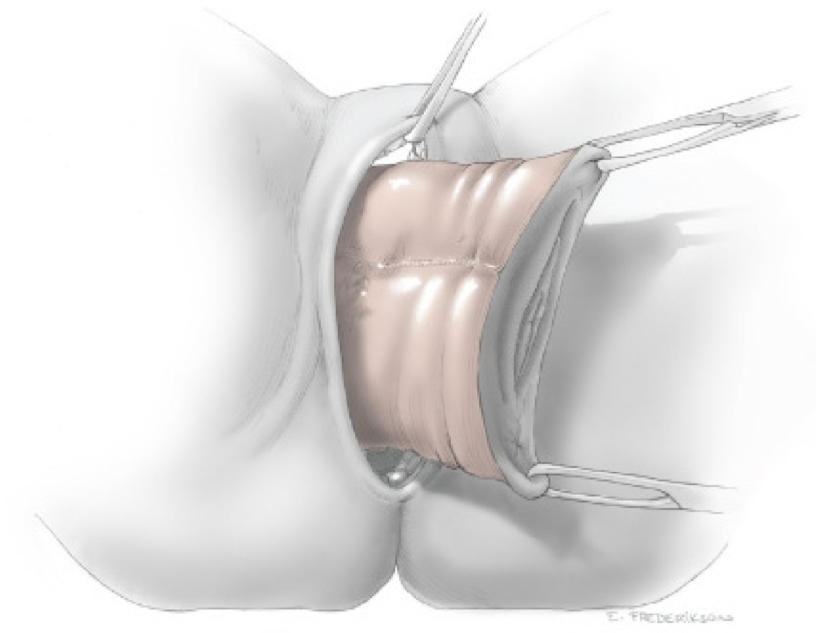
FIGURE 43-3.11

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Infralevator exenteration: connecting the perineal and abdominal spaces.

15. **Infralevator Exenteration: Removal of the Specimen.** Circumferential dissection will result in complete detachment of the specimen, which can be removed either vaginally or abdominally (Fig. 43-3.12). Hemostasis then is achieved with a series of sutures, vascular clips, or clamps and ties. The pelvic floor is inspected carefully and pedicle sites reviewed (Fig. 43-3.13).

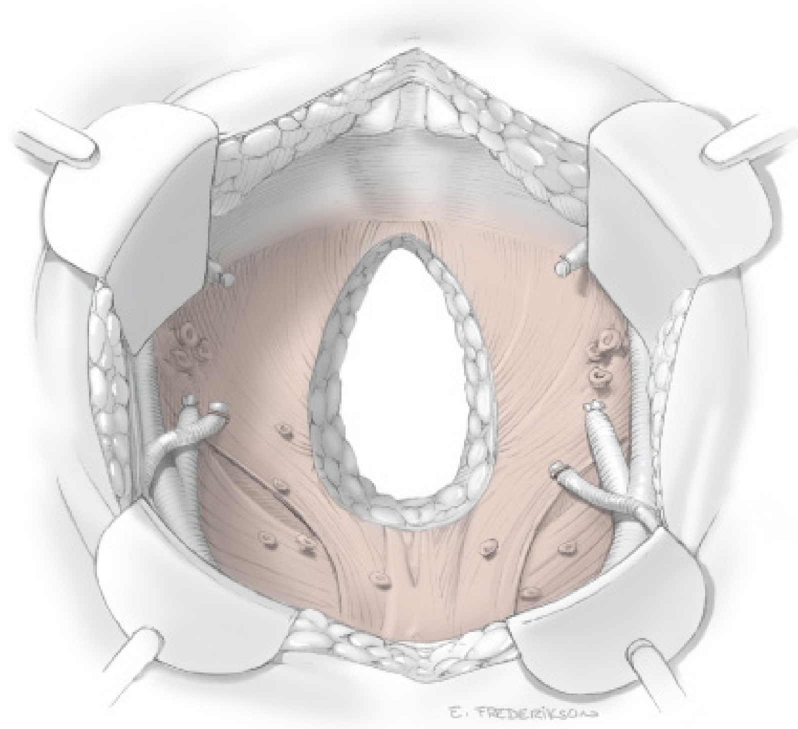
FIGURE 43-3.12



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Infralevator exenteration: removal of the specimen.

FIGURE 43-3.13



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Infralevator exenteration: pelvic floor.

16. **Infralevator Exenteration: Simple Closure.** The most straightforward and quickest way to close the perineum is for the second team to perform a layered closure of the deep tissues with delayed-absorbable suture (Fig. 43-3.14).

    The perineal skin is closed with a delayed-absorbable suture in a running fashion.

FIGURE 43-3.14

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Infralevator exenteration: simple perineal closure.

17. **Final Steps.** A dry laparotomy pad may be held firmly deep in the pelvis to tamponade surface oozing while the conduit, colostomy or bowel anastomosis, and other surgical procedures are performed. An omental J-flap may provide additional blood supply to the irradiated, denuded pelvic floor (see Section 43-8, Vaginal Reconstruction). The type of postoperative suction drainage may be dictated by these ancillary procedures but should be used judiciously (Goldberg, 2006).

Postoperative

The morbidity of total pelvic exenteration depends on a variety of factors: preoperative health of the patient, intraoperative events, extent of the procedure, ancillary procedures, and postoperative vigilance. Hospitals that treat a relatively high volume of such patients report lower surgical in-hospital mortality rates (Begg, 1998).

The immediately life-threatening concerns are massive bleeding, adult respiratory distress syndrome, pulmonary embolism, and myocardial infarction (Dottino, 1995; Finan, 1996; Wydra, 2006). Every effort should be made to encourage early ambulation as soon as the patient is stabilized. A prolonged ileus or small bowel obstruction typically will respond to expectant management but may require initiation of total parenteral nutrition. Intestinal fistulas and leaks are more common when using mesh to cover the pelvic floor or when performing low rectal anastomoses. Omental pedicle grafts and rectus abdominis or gracilis myocutaneous flaps may prevent such complications (see Section 43-8, Vaginal Reconstruction) (Goldberg, 2006; Miller, 1995b). Pelvic abscess and septicemia are additional subacute complications that occur commonly.

43-4 ANTERIOR PELVIC EXENTERATION

Removal of the uterus, vagina, bladder, urethra, distal ureters, and parametrial tissues with preservation of the rectum is meant to be a less morbid operation than total pelvic exenteration. Patients need to be very carefully selected for this more limited procedure to still achieve negative margins. For this reason, women who have previously had a hysterectomy usually are not good candidates.

The most common indications include small recurrences confined to the cervix or anterior vagina after pelvic radiation. In gynecologic oncology, approximately 15 percent of exenterations are anterior (Crozier, 1995; Morley, 1989).

Preoperative

The preoperative evaluation is similar to that described for total pelvic exenteration (see Section 43-3, Total Pelvic Exenteration). Although preservation of the rectum is planned, patients should be advised during the consenting process that potentially unforeseen clinical circumstances may dictate bowel resection and colostomy or low rectal anastomosis. Accordingly, a complete bowel preparation is mandatory.

Intraoperative

Surgical Steps

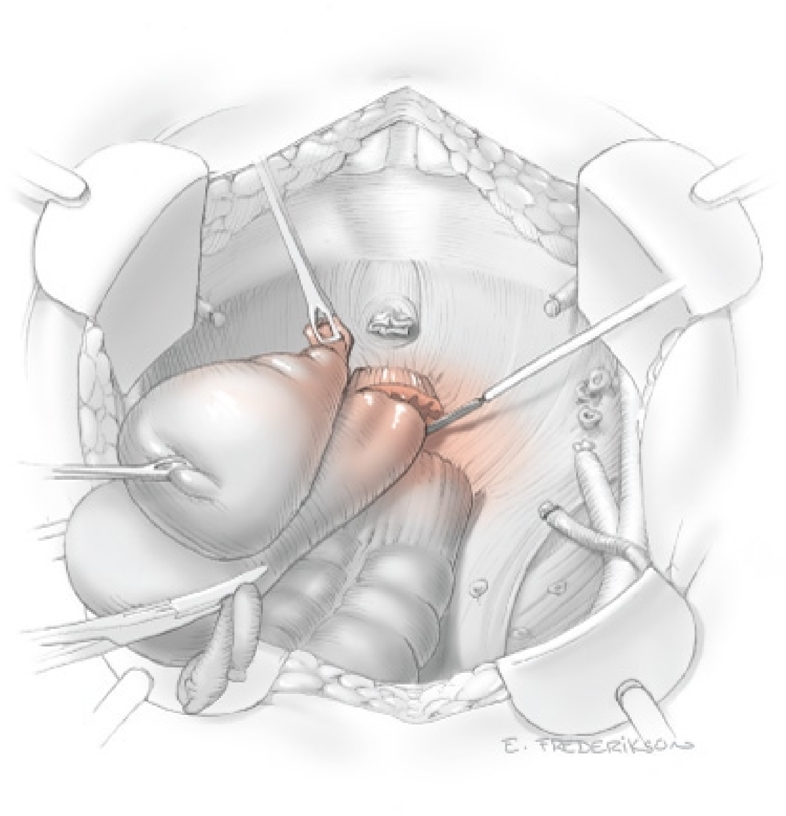
1. **Initial Steps.** Anterior exenteration is technically similar to total pelvic exenteration, described earlier. Patients are positioned in Allen stirrups, the appropriate skin incision is made, the abdomen is explored, lymph nodes are removed, and spaces are developed to exclude metastatic or unresectable disease (see Section 43-3, Total Pelvic Exenteration, Steps 1-5). The procedure begins to differ after the bladder has been mobilized. The surgeon then decides to leave the rectum intact and proceed with anterior pelvic exenteration.

2. **Developing the Rectovaginal Space.** Instead of mobilizing the rectum and dividing the sigmoid, the rectovaginal space is developed much like in a type III radical hysterectomy (see Section 43-1, Radical Abdominal Hysterectomy (Type III), Step 12). The uterosacral ligament and the entire length of the rectal pillars are divided to free the exenteration specimen posteriorly (see Fig. 43-1.7).

3. **Lateral Pelvic Attachments.** The mobilized bladder and uterus are held medially to aid isolation of the cardinal ligaments, internal iliac vessels, and ureter. These structures are successively clamped, cut, and individually ligated (see Section 43-3, Total Pelvic Exenteration, Steps 8-9).

4. **Removal of the Specimen.** After the anterior pelvic exenteration specimen has been mobilized completely, the urethra and vagina are divided (Fig. 43-4.1). The vaginal cuff is closed with delayed-absorbable suture in a running fashion (Fig. 43-4.2). Similarly, the urethra is closed with a running suture using delayed-absorbable suture. Creation of a urinary conduit follows as described in Section 43-6, Incontinent Urinary Conduit and 43-7, Continent Urinary Conduit.

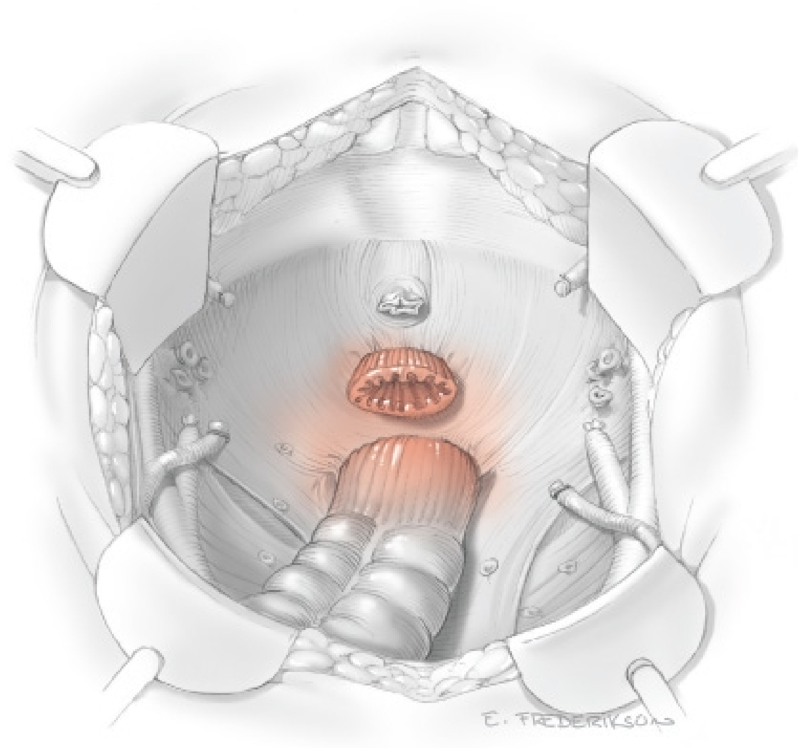
FIGURE 43-4.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Removal of the specimen.

FIGURE 43-4.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Appearance of the pelvic floor.

5. **Final Steps.** Typically, the lesion is small and lies above the levators; thus, a perineal phase is not required. Placement of a myocutaneous flap for vaginal reconstruction may be more problematic in these patients due to limited space in the pelvis.

Postoperative

Morbidity of anterior pelvic exenteration is comparable with that for total pelvic exenteration (Sharma, 2005). Ideally, the operation is shorter, and restoration of bowel function is more rapid. Some patients will experience tenesmus or long-term rectal symptoms that likely stem from interruption of the autonomic nervous system in surrounding tissue.

43-5 POSTERIOR PELVIC EXENTERATION

Removal of the uterus, vagina, rectum, and parametrial tissues with preservation of the ureters and bladder is meant to be a less morbid operation than total pelvic exenteration. Patients should be selected carefully for this more limited procedure to still achieve negative margins. For this reason, women who have previously had a hysterectomy usually are not good candidates. The most common indications include small postirradiation recurrences involving primarily the posterior vaginal wall or co-existing with a rectovaginal fistula. In gynecologic oncology, fewer than 10 percent of exenterations are posterior (Berek, 2005; Crozier, 1995).

Preoperative

Preoperative evaluation is largely identical to that described for total pelvic exenteration (see Section 43-3, Total Pelvic

Exenteration). The surgeon's judgment and experience are critical in deciding to proceed with a more limited operation. However, patients should be advised during the consenting process that potentially unforeseen clinical circumstances may dictate resection of the ureters and bladder with formation of a urinary conduit (see Sections 43-6, Incontinent Urinary Conduit and 43-7, Continent Urinary Conduit).

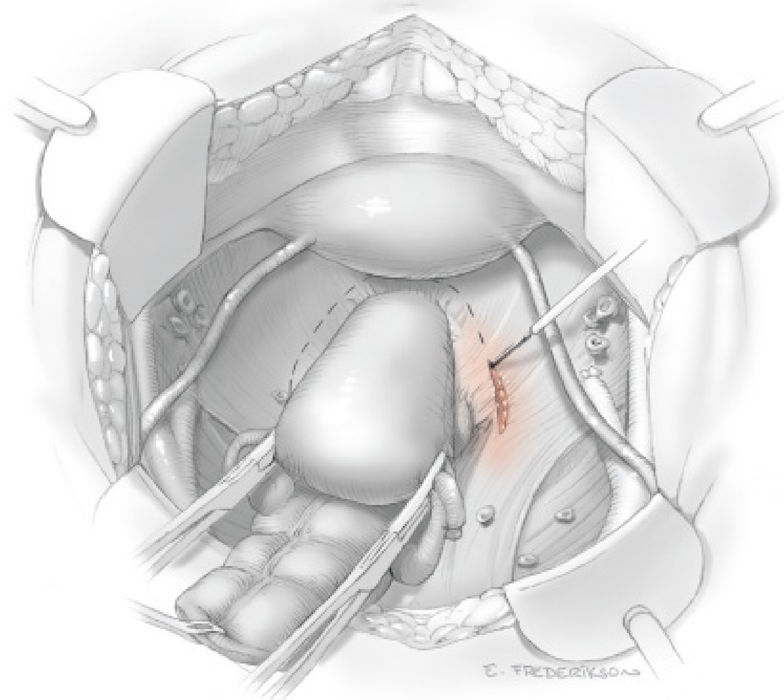
Intraoperative

Surgical Steps

1. **Initial Steps.** Posterior pelvic exenteration is technically similar to a type III radical hysterectomy but with the addition of a more extended vaginectomy and rectosigmoid resection (see Section 43-1, Radical Abdominal Hysterectomy (Type III)). The operation begins as a total pelvic exenteration. Patients are positioned in Allen stirrups, the appropriate skin incision is made, the abdomen is explored, lymph nodes are removed, and spaces are developed to exclude metastatic or unresectable disease (see Section 43-3, Total Pelvic Exenteration, Steps 1-5). The surgeon then decides whether to leave the bladder intact and proceed with posterior exenteration.

2. **Ureteral Dissection.** The ureters are mobilized, uterine arteries are ligated at their internal iliac origin, and parametrial tissue is divided at the pelvic sidewall (see Section 43-1, Radical Abdominal Hysterectomy (Type III), Steps 4-8). The bladder then is dissected distally to aid in unroofing the ureters from the parcervical tunnels much like in a type III radical hysterectomy (see Section 43-1, Radical Abdominal Hysterectomy (Type III), Steps 9-11). The lateral attachments have been clamped, cut, and tied with delayed-absorbable suture all the way to the levator ani muscles (Fig. 43-5.1). However, typically these steps are more tedious in a previously irradiated field because of tissue fibrosis and scarring.

FIGURE 43-5.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

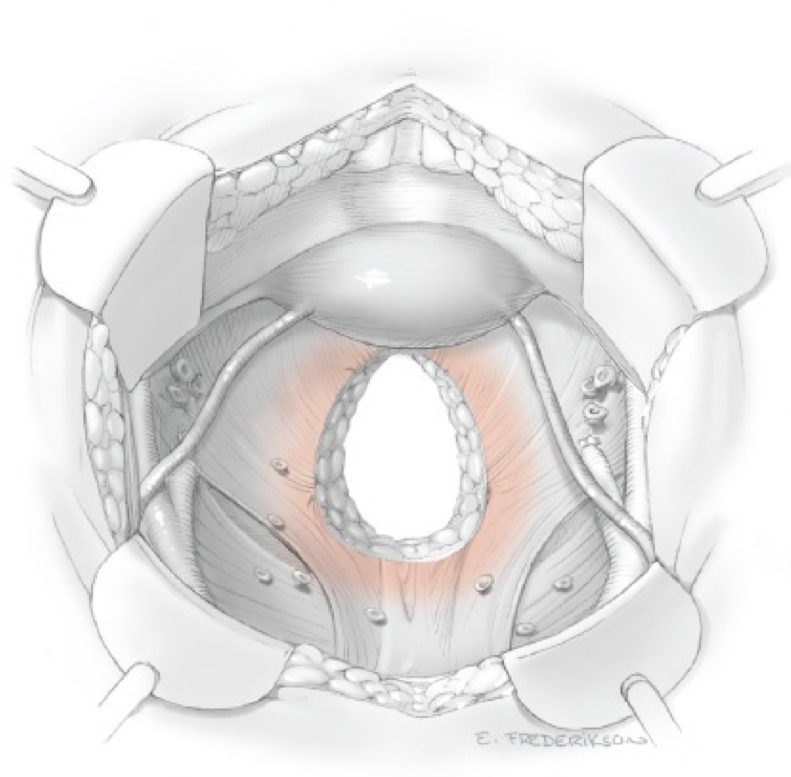
Incising the levator muscles.

3. **Mobilizing the Rectum.** The sigmoid is divided with the mesentery and peritoneal attachments, as described earlier for a total pelvic exenteration (see Section 43-3, Total Pelvic Exenteration, Step 7). The retrorectal space is dissected bluntly to mobilize the rectum and enable transection of the rectal pillars (see Fig. 43-3.5).

4. **Removal of the Specimen.** The dissection is continued circumferentially to (or through) the levator ani muscles to encompass the tumor (Fig. 43-5.2).

   The distal vagina is transected and sewn closed. The entire specimen then may be placed on traction to aid placement of the transverse anastomosis (TA) stapler and division of the rectum. The rectum is divided below the tumor, and the specimen is removed.

FIGURE 43-5.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Specimen removed.

5. **Final Steps.** Typically, the lesion is small and lies above the levator ani muscles. Thus, for these cases, a perineal phase is not required. Placement of a myocutaneous flap for vaginal reconstruction may be more problematic in such patients due to limited space in the pelvis. The sigmoid colon is removed from the upper abdomen, and colostomy or rectosigmoid anastomosis is completed.

Postoperative

Morbidity of posterior pelvic exenteration is comparable with that of total pelvic exenteration (Sharma, 2005). Ideally, the operation is shorter and urinary complications are less frequent. However, posterior exenteration in a previously irradiated patient frequently results in a contracted bladder and intractable urinary incontinence.

43-6 INCONTINENT URINARY CONDUIT

Removal of the bladder during total or anterior exenteration is the main indication for an incontinent urinary conduit. Less commonly, an otherwise irreparable postirradiation vesicovaginal fistula may warrant urinary diversion. Following cystectomy, a resected segment of bowel that maintains its mesenteric and vascular connections is used as a new reservoir. A stoma is crafted between the bowel segment and an opening in the anterior abdominal wall. Ureters are re-implanted into this portion of bowel.

Various diversion techniques are available to create such urinary conduits. These are categorized as *incontinent diversions or continent diversions.* Incontinent diversion is the simplest to create, but postoperatively, a patient must wear an ostomy bag continuously. These conduits often are preferable for medically compromised patients, the elderly, and anyone with a short life expectancy. Alternatively, a continent urinary reservoir can be created that is emptied by intermittent patient self-catheterization of the bowel stoma.

Of incontinent diversions, an *ileal conduit* historically has been the most common urinary diversion used in gynecologic oncology (Orr, 1982b). However, the bowel segment and distal ureters invariably lie within the radiated field, which may lead to higher rates of stenosis or leakage at the ureteral anastomotic sites. More recently, *the transverse colon conduit* has proven to be a very successful alternative for previously irradiated patients (Segreti, 1996a; Soper, 1989). *Sigmoid conduits* generally are less desirable owing to pre-existing radiation damage and proximity to a colostomy site. The *jejunal conduit* is another rarely used option outside the radiation field. In these patients, the shortest possible segment should be used to decrease the characteristic electrolytic syndrome of hypochloremic acidosis with hyponatremia, hyperkalemia, and uremia (Golimbu, 1975; Klein, 1986).

The basic principles of constructing an incontinent urinary conduit are the sameâ€"regardless of the intestinal segment used. First, healthy-appearing bowel should be selected with a good blood supply. Second, wide ureterointestinal anastomoses and stenting are essential to minimize the risk of stenosis. Third, sufficient mobility of the ureters and bowel segment is important to prevent any tension that might lead to anastomotic leaks. Fourth, creation of a straight tunnel through the abdominal wall will prevent obstruction.

Preoperative

PATIENT EVALUATION

The preoperative evaluation usually is dictated by the preceding exenterative procedure. The specific decision is whether to plan for an incontinent or continent urinary conduit. Patients should be counseled extensively about the differences. The type of conduit selected should be considered permanent, although later conversions are possible (Benezra, 2004).

CONSENT

Patients should be advised that intraoperative findings may dictate revision of an original surgical plan. Postoperatively, urinary infections with or without pyelonephritis are common. Anastomotic leaks are less frequent with routine ureteral stent placement but are potentially problematic (Beddoe, 1987). Episodes of small bowel obstruction are possible. In the long term, strictures and stenoses may cause renal compromise. Infrequently, re-operation is necessary for complications that do not respond to conservative management (Houvenaeghel, 2004).

PATIENT PREPARATION

Bowel preparation obviously is mandatory, but preparation typically is dictated by the preceding exenterative surgery. Ideally, an enterostomal therapist is available to mark a conduit stoma site. This site should be unobstructed in the supine, sitting, and standing positions.

Intraoperative

Surgical Steps

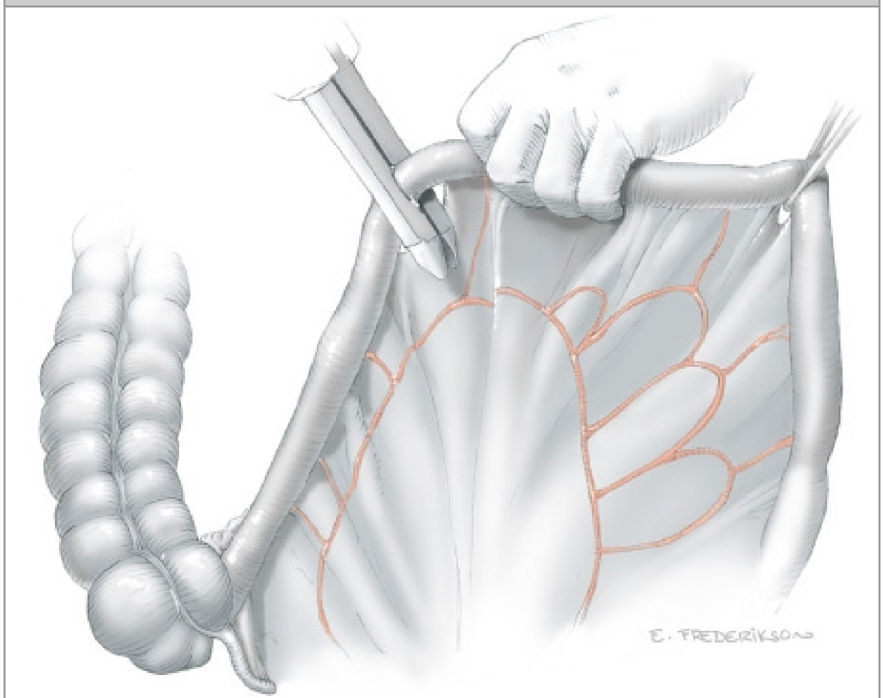
1. **Initial Steps.** The incontinent urinary conduit is constructed as the last major intra-abdominal procedure during exenterative surgery to avoid unnecessary traction on the anastomoses. Hemostasis should be achieved before beginning the conduit. Anesthesia requirements, patient positioning, and skin incisions typically are dictated by the preceding operation.

2. **Exploration.** The bowel segment should be inspected carefully at the planned conduit site. It must be healthy appearing, not tethered, and lie within range of the distal ureters. The final decision now is made about which type of incontinent conduit is best for the circumstances. If the distal ileum has the typical leathery, pale, mottled appearance of radiation injury, a conduit should be prepared from the transverse colon. Overlooking the importance of this decision can lead to a variety of otherwise preventable complications intraoperatively and postoperatively.

3. **Ileal Conduit: Preparing the Bowel Segment.** The ileocecal junction is located, and the ileum is elevated proximally. A bowel section is identified with the most mobility to reach the right side of the abdominal wall where the stoma will be located. Ideally, this section begins 25 to 30 cm from the ileocecal valve. The mesentery is scored with an electrosurgical blade on each side at this point to aid insertion of a hemostat directly beneath the ileal serosa. A Penrose drain is pulled through to mark the section of bowel that will become the abdominal wall stoma.

   The conduit length depends on subcutaneous tissue depth and ileum mobility but should measure approximately 15 cm. The conduit's proximal end is selected by measuring the ileum that lies distal to the Penrose drain, and again, the mesentery is scored. The gastrointestinal anastomosis (GIA) stapler then is inserted to divide the distal bowel segment (Fig. 43-6.1). The point of division ideally should be at least 12 cm from the ileocecal valve. Intestinal continuity, minus the excised segment, is re-established anterior to the conduit with a functional end-to-end anastomosis using the GIA and transverse anastomosis (TA) staplers (see Figs. 43-18.2 and 43-18.3). The conduit mesentery is divided carefully. The vasculature may be compromised if too much mesentery is divided, whereas too little will result in tension on the conduit. A perfect balance is required.

FIGURE 43-6.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Ileal conduit: preparing the bowel segment.

4. **Ileal Conduit: Preparing the Ureters.** The staple line is excised from the stomal end of the conduit, and the conduit is irrigated. The ureters should be engorged from clips placed earlier during exenteration (see Section 43-3, Total Pelvic Exenteration, Step 9). The distal end of the ureters never should be grasped directly with forceps or handled roughly to prevent focal necrosis that may impede successful anastomosis. They are freed from their retroperitoneal attachments so that they easily reach past the point of their planned anastomosis into the conduit.

5. **Ileal Conduit: Ureteral Anastomoses.** Adson forceps are used to grasp a small section of the ileal serosa where the left ureter will reachâ€"ideally approximately 2 cm from the proximal conduit's end on the anterior side of the antimesenteric

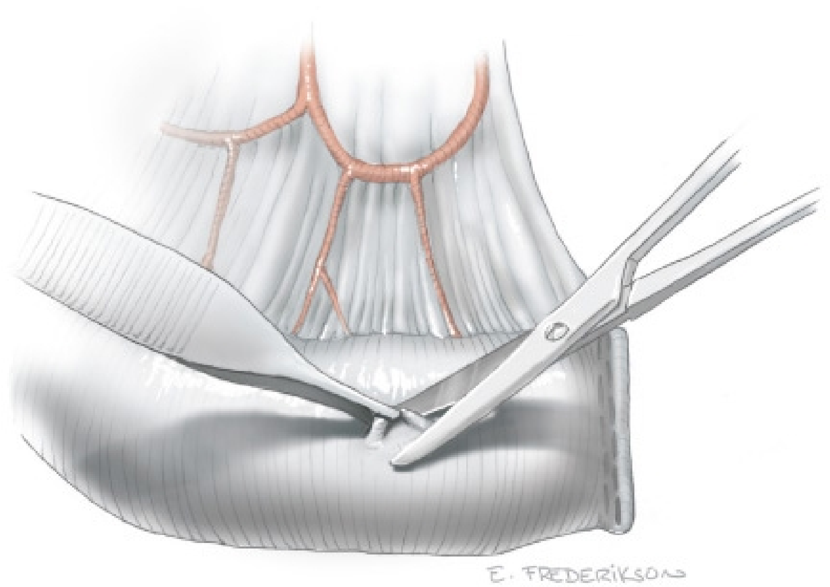
surface. At this site, Metzenbaum scissors remove a small full-thickness section of bowel wall (Fig. 43-6.2). The ileal mucosa should be easily visible.

The distal tip of the left ureter is cut at a 45-degree angle just in front of the previously placed clip. If the distal ureters exhibit fibrosis, they are trimmed to reach healthy tissue. Urine will drain into the abdomen while a 4-0 delayed-absorbable stay suture is placed from outside through the ureter's distal tip. The needle is left on this traction stitch because it will be the final suture in the anastomosis. Fine-tip scissors are used to spatulate the ureter for 1 cm (Fig. 43-6.3). This maneuver may reduce the possibility of future stenosis.

The first suture is placed at the apex of the spatulation with a full-thickness bite through the ureteral wall and bowel mucosa (Fig. 43-6.4). Two or three additional sutures are placed. The ileal mucosa must be included in each stitch for best results. A 6F or 7F ureteral stent then is placed through the stoma and advanced through the anastomosis into the left renal pelvis. This is held against the wall of the conduit with one hand and secured with a 3-0 or 4-0 plain catgut suture through the entire bowel wall around the stent to hold it in place. The left ureteral anastomosis is completed with additional sutures.

The entire procedure then is repeated on the right. Saline with methylene blue dye may be used to fill the conduit and observe for anastomotic leaks.

FIGURE 43-6.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

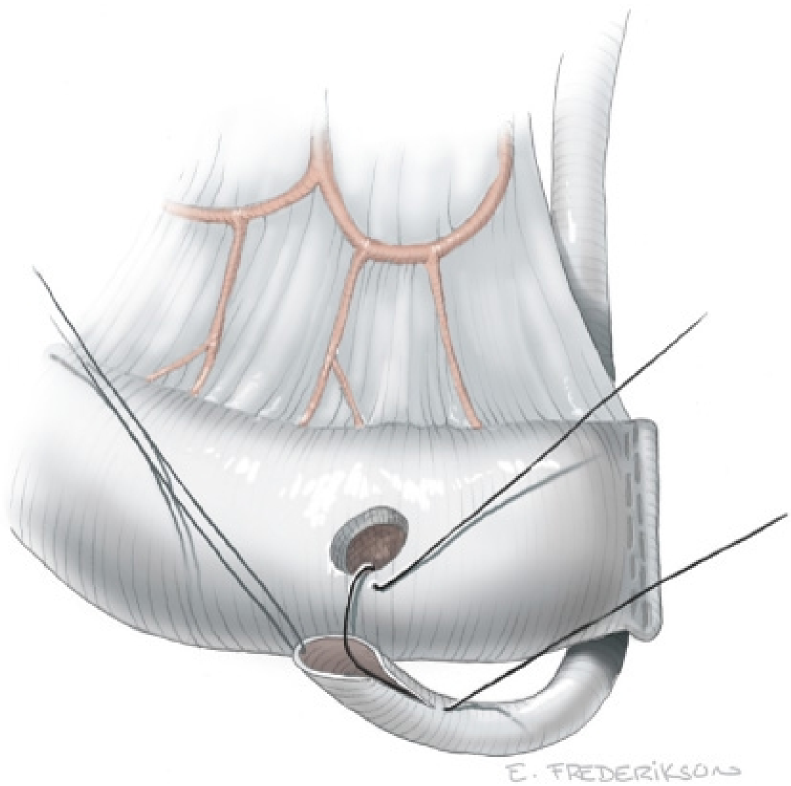
Ileal conduit: ileal incision.

FIGURE 43-6.3

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Ileal conduit: spatulating the ureter.

FIGURE 43-6.4



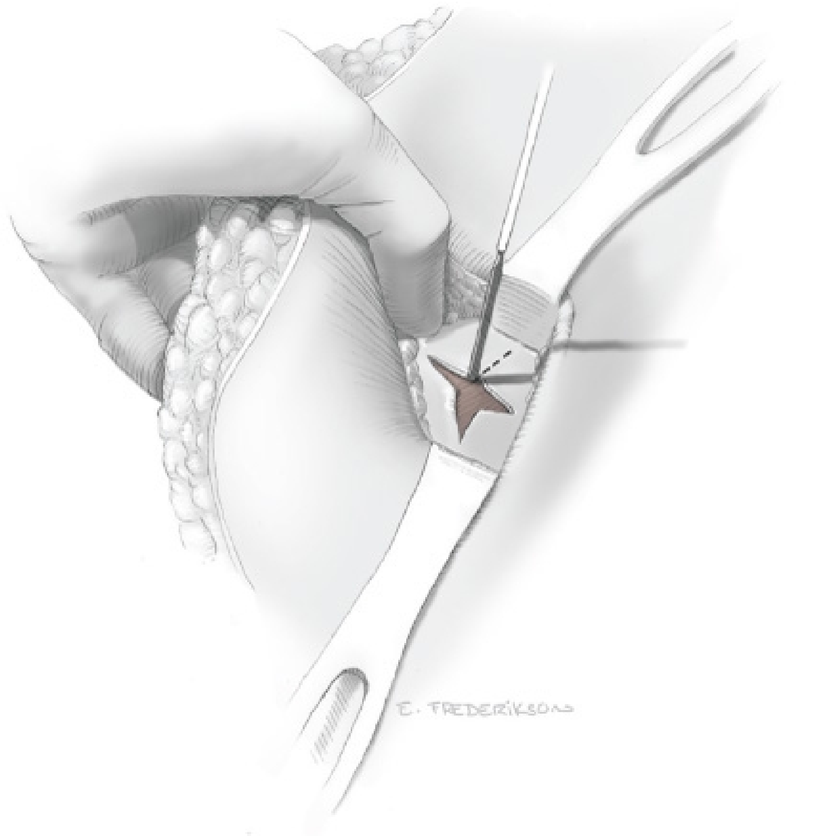
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Ileal conduit: suturing ureter and ileal segment.

6. **Ileal Conduit: Stoma Creation.** The skin at the proposed stoma site is elevated with a Kocher clamp. An electrosurgical blade, set on cutting mode, is used to excise a small circle of skin. The subcutaneous fat is separated by blunt dissection until the fascia is visible. A cruciate incision is made with an electrosurgical blade (Fig. 43-6.5). The rectus abdominis muscle is split longitudinally, and another cruciate incision is created in the peritoneum. The opening is expanded bluntly until it easily accommodates two fingers.

   The proximal conduit and stents are carefully pulled through the incision until at least 2 cm of ileum protrudes through the skin (Fig. 43-6.6). The mesentery may need to be trimmed or the abdominal wall opening further dissected to accommodate the conduit. The mucosal edge is everted. The stoma is completed with "rosebud" 3-0 delayed-absorbable stitches, which incorporate the ileal mucosa, intervening bowel serosa, and skin dermis (Fig. 43-6.7). Circumferential sutures are placed. To enable correct identification postoperatively, the right ureteral stent is cut at a right angle.

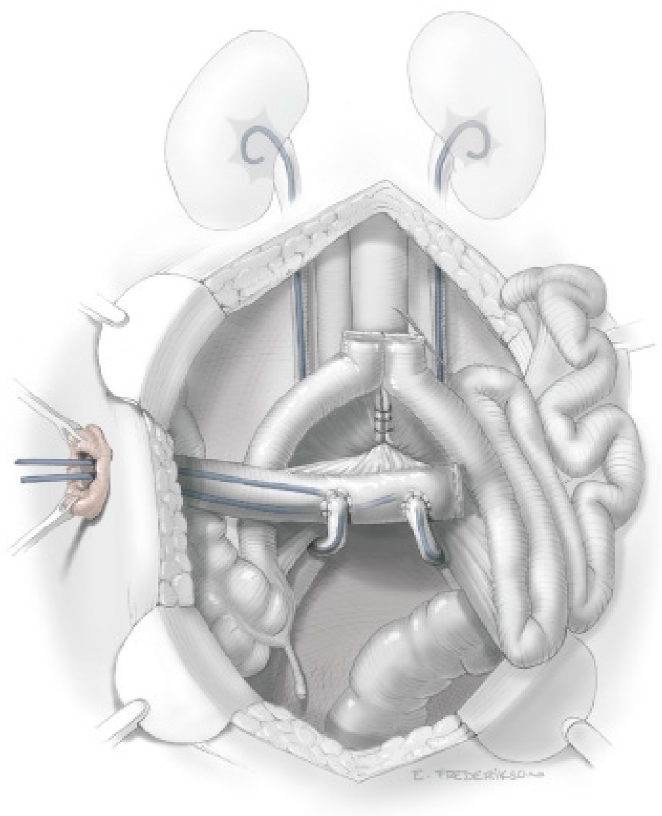
FIGURE 43-6.5



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Ileal conduit: making the stoma.

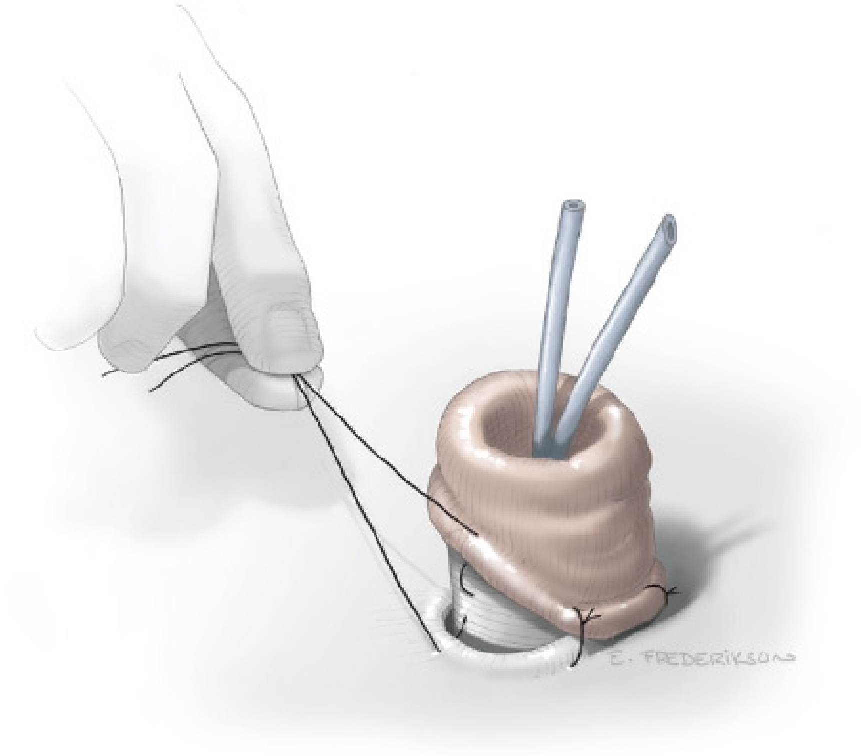
FIGURE 43-6.6



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Ileal conduit: stoma with stents is carefully pulled through the incision.

FIGURE 43-6.7



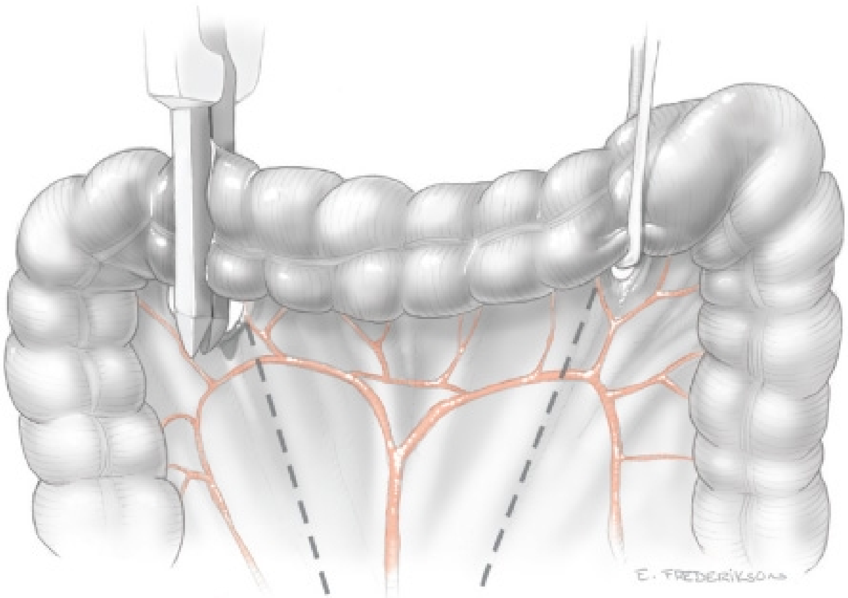
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Ileal conduit: suturing the stoma.

7. **Transverse Colon Conduit.** For this type of conduit, the hepatic and splenic flexures of the transverse colon generally must be mobilized. In addition, the right side of the omentum is detached. Division points are marked with Penrose drains and transected (Fig. 43-6.8). The mesocolon then is divided to the posterior abdominal wall.

   Intestinal continuity is re-established anterior to the conduit by a functional end-to-end anastomosis created using EEA and TA staplers. Ureters are sufficiently mobilized to reach the conduit. The ureteral anastomoses then are completed over stents (Beddoe, 1987). The stoma is made almost anywhere that the conduit will comfortably reach. The stomal end of the conduit is brought through the abdominal wall and secured (Fig. 43-6.9).

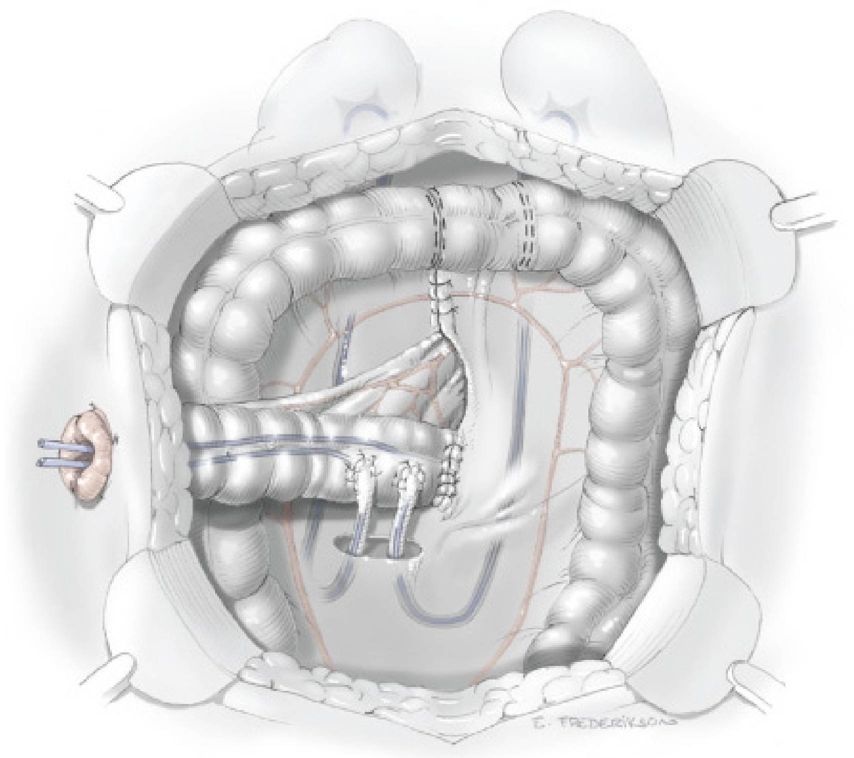
FIGURE 43-6.8



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Transverse colon conduit: preparing the bowel segment.

FIGURE 43-6.9



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Transverse colon conduit: final appearance.

8. **Final Steps.** To prevent postoperative sliding and ultimate tension on the anastomoses, the conduit's proximal end is secured to the posterior peritoneum with interrupted delayed-absorbable suture. Mesenteric defects require closure to prevent internal hernias, but not so tightly as to compromise blood supply. A suction drain may be placed if there is concern about the integrity of the anastomoses. The ureteral stent tips are cut to fit into the stoma appliance in a manner to differentiation which stent is on the right (cut at a right angle) and which is on the left (cut off straight). If the stoma appears dusky, the abdominal wall tunnel may be too tight, the mesentery may be twisted or placed on too much tension, or the blood supply may not be sufficient. The worst circumstance is the latter, and this generally requires the entire conduit to be redoneâ€”but may prevent catastrophic later complications.

Postoperative

The stoma should be checked regularly for viability during the immediate postoperative recovery period. Both stents should be functioning. A dry stent that does not respond to irrigation should prompt an imaging study to exclude obstruction. Urinary fistulas and obstructions are uncommon, but they are potentially life-threatening if they are not addressed with percutaneous drainage or re- operation (Bladou, 1995; Lichtinger, 1986). Prolonged bowel dysfunction may indicate an anastomotic urine leak or small bowel obstruction.

Patients often are re-admitted within a few weeks of surgery due to partial small bowel obstruction, urinary infection, wound separation, or other complications of exenteration. These typically resolve with targeted supportive care. Long-term complications include ureteral stenosis and renal loss. Renal function may deteriorate because of infection and reflux. Some patients may require stoma revision secondary to postoperative sloughing or retraction (Hancock, 1986).

Predictably, the overall morbidity of creating an incontinent conduit is much higher in previously irradiated patients (Houvenaeghel,

2004). Tissue quality and mobility are especially important in these patients.

43-7 CONTINENT URINARY CONDUIT

Removal of the bladder during total or anterior exenteration is the main indication for a continent urinary conduit. Vesicovaginal fistulas and disabling incontinence following radiation therapy are other, less common reasons (Lentz, 1995). Following cystectomy, urine is diverted into a reservoir created from a resected bowel segment. Depending on their construction, these diversions may render a woman continent or incontinent. An incontinent conduit reservoir chronically drains into an ostomy bag, whereas a continent conduit does not leak urine. Patients empty the reservoir by intermittent self-catheterization.

Continent conduits, however, may not be appropriate for all patients. The operation is more complex than an incontinent diversion procedure and may lead to more postoperative complications (Karsenty, 2005). They also require a highly motivated patient who is capable of long-term self-catheterization. An ideal candidate for a continent conduit is a young, otherwise healthy woman without a colostomy.

There are several continent diversion methods, and in gynecologic oncology, the continent ileocolonic urinary reservoir (Miami pouch) has become the most popular choice (Salom, 2004). This pouch is technically straightforward to construct and uses tissues that characteristically lie in nonirradiated areas (Penalver, 1998).

A Miami pouch includes a distal ileum segment, the ascending colon, and a portion of transverse colon. The basic steps involve opening the colon segment along the length of the tenia and folding it onto itself. The walls of the ascending and transverse colon are then sewn together to achieve a reservoir with low intraluminal pressure. The ileum segment is tapered, and purse-string sutures are placed at the level of the ileocecal valve to achieve continence. The ileal segment then is exteriorized as a stoma to allow catheterization (Penalver, 1989).

Preoperative

PATIENT EVALUATION

Preoperative evaluation usually is dictated by the preceding exenterative procedure. The specific decision is whether to plan for an incontinent or continent urinary conduit. Patients should be counseled extensively about the differences. The presence of a permanent colostomy removes the apparent advantage of a continent conduit and an abdominal wall without stomas. Moreover, catheterization may be more problematic in very obese women. Some patients with prior high-dose radiation or chronic bowel disease also may not be good candidates.

CONSENT

Patients should be advised that intraoperative findings such as poor bowel appearance and dense adhesions may dictate a change in original surgical plans. In addition, complications are common and should be reviewed. In experienced centers, half of patients will have one or more early pouch-related complications: ureteral stricture with obstruction, anastomotic leak, fistula, difficulty in catheterization, pyelonephritis, or sepsis. One third will develop late complications beyond 6 weeks. Ten percent of patients ultimately will require re-operation to revise the Miami pouch (Penalver, 1998).

PATIENT PREPARATION

Bowel preparation obviously is mandatory, but preparation generally is dictated by the preceding exenterative surgery. Ideally, an enterostomal therapist is available to mark a conduit stoma site. The site should be unobstructed in the supine, sitting, and standing positions.

Intraoperative

Surgical Steps

1. **Initial Steps.** The continent urinary conduit is constructed as the last major intra-abdominal procedure during exenterative surgery to avoid unnecessary traction on anastomoses. Before beginning the conduit, hemostasis should be achieved. Anesthesia requirements, patient positioning, and skin incisions typically are dictated by the preceding operation.

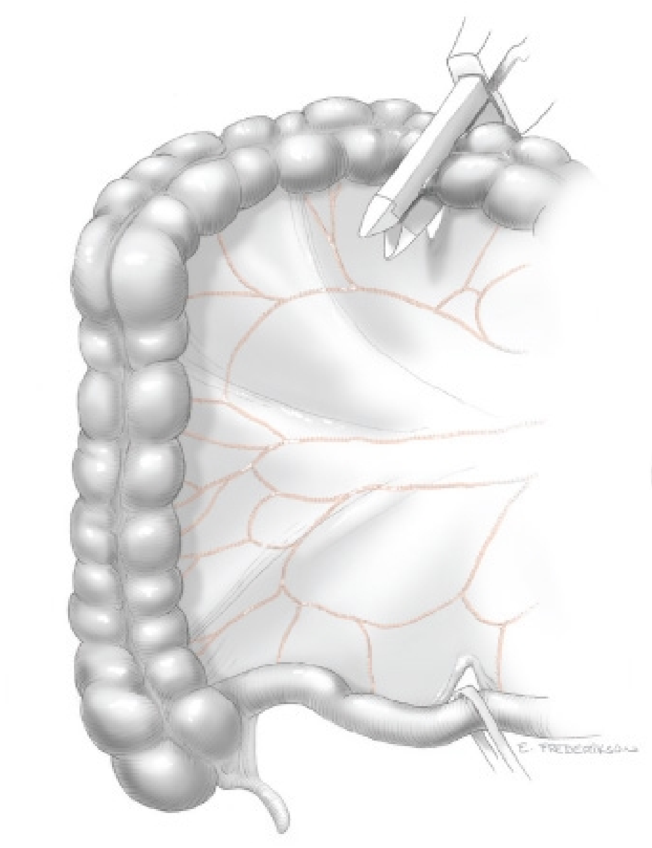
2. **Exploration.** The bowel segment should be inspected carefully at the planned conduit site. It must be healthy appearing without severe radiation injury. At this point, the final decision to proceed with creation of a Miami pouch is made.

3. **Preparing the Bowel Segment.** The right colon is freed from the cecum around the hepatic flexure to the proximal transverse colon along the white line of Toldt. This line is the reflection of posterior abdominal parietal peritoneum over the mesentery of the descending colon. The conduit will require about 25 to 30 cm of colon and at least 10 cm of ileum. With these measurements in mind, a surgeon selects sites to divide the bowel (Fig. 43-7.1).

   The mesentery is scored with an electrosurgical blade, and a Penrose drain is placed around the sections to be divided. Within the mesentery, the underlying vasculature is reviewed to ensure sufficient conduit blood supply. A GIA stapler is used to divide the bowel at both sites marked with the Penrose drains (see Fig. 43-7.1).

   The mesenteries are incised down through the avascular areas to the posterior peritoneum. At this point, intestinal continuity is re-established by a functional end-to-end stapled ileotransverse enterocolostomy using the GIA and TA staplers. The mesenteric defect is closed with delayed-absorbable suture in a running fashion.

FIGURE 43-7.1



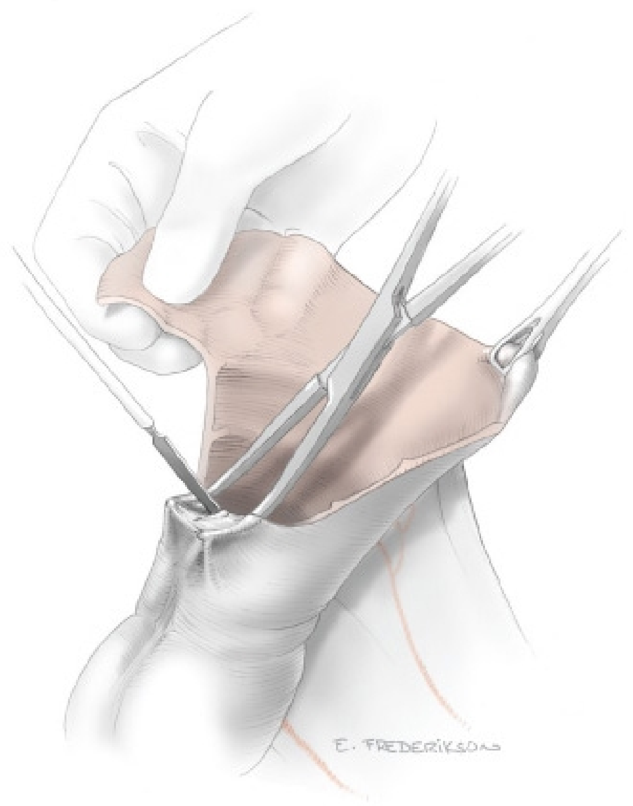
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Preparing the bowel segment.

4. **Detubularizing the Bowel.** The conduit staple lines are removed with Metzenbaum scissors, and the bowel is irrigated into a basin. Of this bowel segment, the entire colon portion is opened with an electrosurgical blade along the tenia of the

antimesenteric border to "detubularize" the bowel and remove the appendix (Fig. 43-7.2).

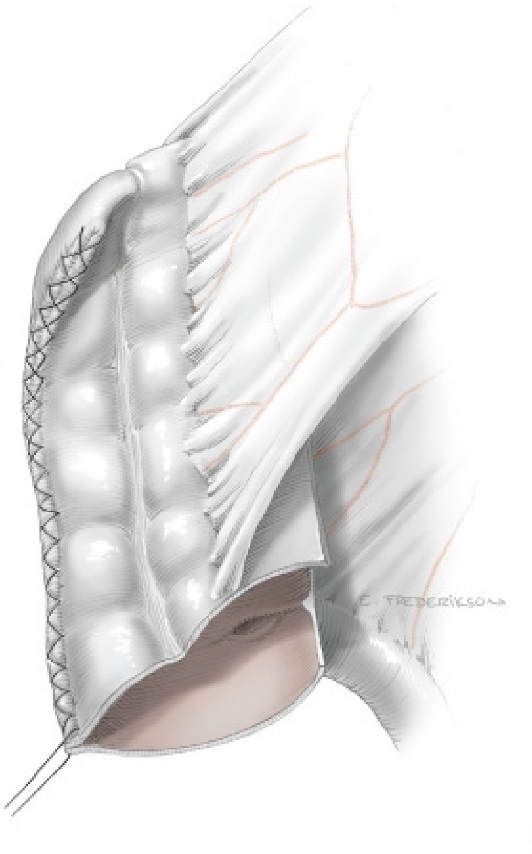
FIGURE 43-7.2



Detubularizing the bowel.

5. **Creating the Pouch.** The colon segment is folded in half, and four delayed-absorbable stay sutures are placed at the corners to begin creation of the pouch. One lateral edge is closed in two layers with 2-0 and 3-0 delayed-absorbable suture in a running fashion (Fig. 43-7.3).

FIGURE 43-7.3

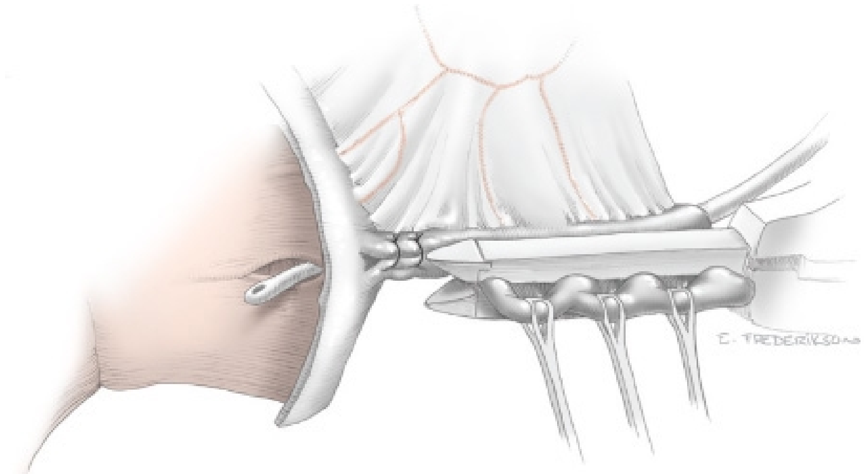


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Creating the reservoir.

6. **Tapering the Ileum.** A 14F red rubber catheter is inserted through the terminal ileum segment into the pouch. Two purse-string delayed-absorbable sutures are placed 1 cm apart at the ileocecal junction. The ileum is elevated with Babcock clamps, and a GIA stapler is used to taper the terminal ileum on its antimesenteric border over the catheter (Fig. 43-7.4). An abdominal wall opening is made in the right lower quadrant so that the ileal segment of the conduit can be pulled through to approximate its final position (see Figs. 43-6.5 and 43-6.6).

FIGURE 43-7.4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

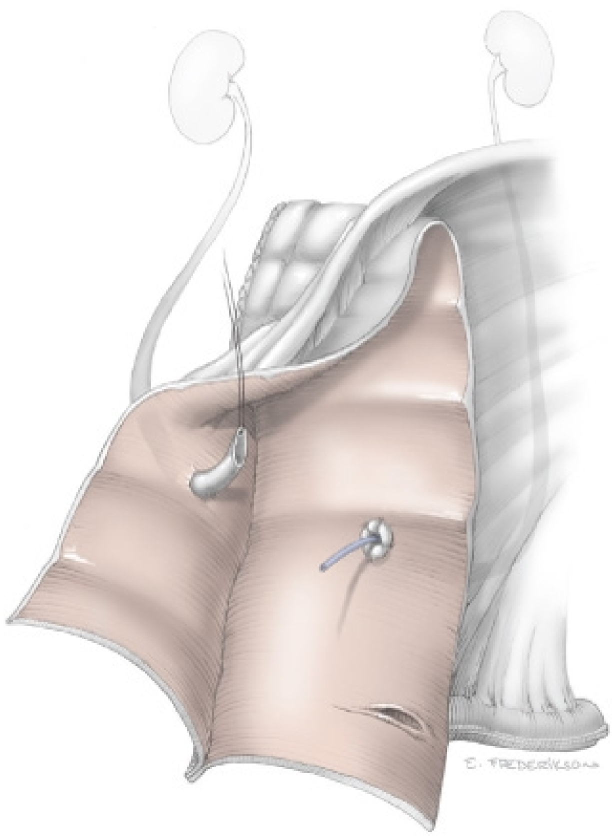
Tapering the ileum.

7. **Ureteral Anastomoses.** Both ureters are further mobilized from their retroperitoneal attachments and brought into position under the ascending mesocolon. To avoid crush injury and subsequent necrosis, they never should be grasped or handled roughly. Their anastomotic sites to the pouch are selected based on ureter length and their ability to have a straight course to the pouch.

   One ureter usually is brought through on either side of the posterior pouch suture line. The ureters are trimmed and spatulated (see Fig. 43-6.3). The bowel mucosa is incised away from the suture line (see Fig. 43-6.2). A hemostat is poked through the bowel wall to bring 2 cm of each ureter into the pouch by pulling on the traction suture (Fig. 43-7.5).

   Each ureter is secured to the bowel mucosa with interrupted stitches of 4-0 delayed-absorbable suture. Ureteral stents (6F or 7F) are inserted and sutured to the bowel wall with 3-0 plain catgut to stabilize their placement.

FIGURE 43-7.5

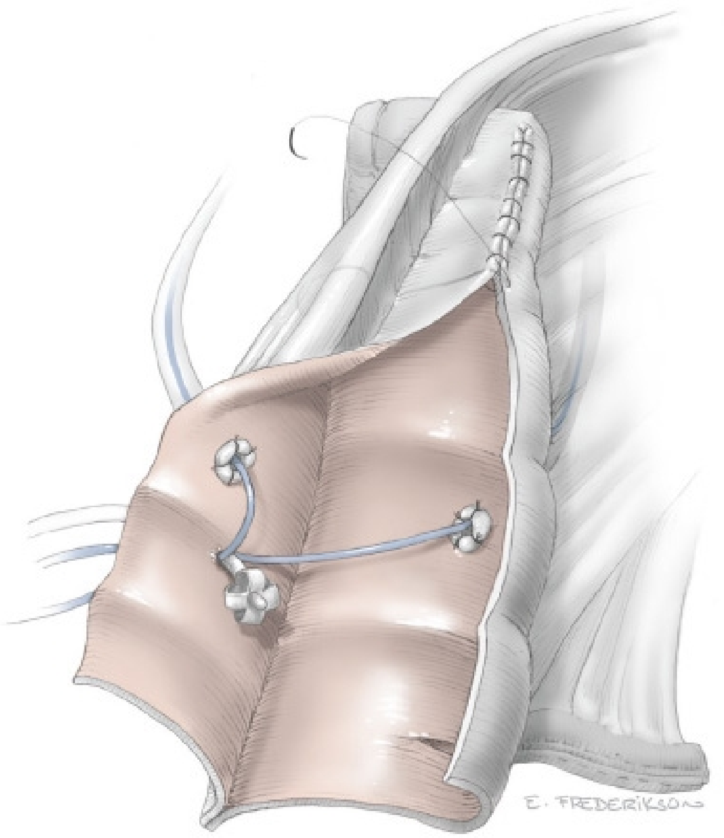


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Ureteral anastomoses.

8. **Closing the Pouch.** A large Malecot catheter is brought into the pouch away from the ileocecal valve. The ureteral stents are brought out through the pouch next to the Malecot (Fig. 43-7.6). A watertight purse-string 3-0 plain catgut suture is placed where the catheters exit the pouch. The remaining lateral edges of the pouch are sutured closed with two layers of 2-0 and 3-0 delayed-absorbable suture in a running fashion. Continence may be tested by filling the pouch with 250 to 300 mL of saline and removing the red rubber catheter (Fig. 43-7.7). Additional purse-string sutures may be placed at the ileocecal valve if incontinence is demonstrated.

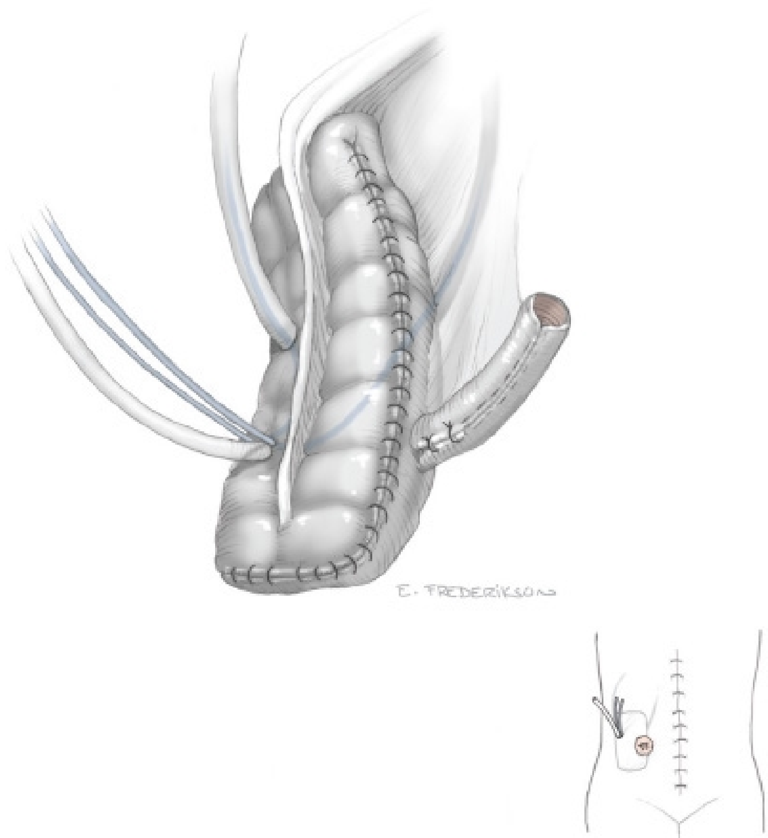
FIGURE 43-7.6



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Closing the reservoir.

FIGURE 43-7.7



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Final steps.

9. **Final Steps.** The ileal segment is pulled through the abdominal wall and may require trimming to sit flush. The stoma is created by placing interrupted stitches of 3-0 delayed-absorbable suture between the dermis and ileal mucosa. A red rubber catheter should be inserted and withdrawn to make sure that the pouch can be accessed easily. A Jackson-Pratt (JP) drain then is placed near the pouch and brought out through a separate stab wound away from the stoma.

   The two stents and Malecot drain are brought out through a separate stab wound away from the stoma site and individually fixed to the skin with nylon sutures. These will be removed later postoperatively.

Postoperative

The Miami pouch initially requires more care than an incontinent urinary conduit. Mucus will be produced by the colonic bowel segment. Therefore, the Malecot catheter should be irrigated every few hours to permit urine drainage. In contrast, the ureteral stents are irrigated only if one of the catheters becomes obstructed. Two to 3 weeks postoperatively, an intravenous pyelogram (IVP) and gravity pouchogram should be performed. If these tests are normal, the ureteral stents, Malecot catheter, and JP suction drainage tube all may be removed.

The patient may be taught self-catheterization using an 18F to 22F red rubber catheter and antiseptic technique. Catheterizations may be progressively spaced over weeks to finally be required only every 6 hours during the day and not at night. In addition, the pouch requires periodic irrigation to remove mucus. An IVP, pouchogram, and serum electrolytes and creatinine determinations are performed at 3 months postoperatively and then every 6 months to evaluate the pouch, renal function, and upper urinary tracts.

More than half of patients will have a conduit-related complication postoperatively. Fortunately, most may be managed successfully conservatively without the need for re-operation (Ramirez, 2002). The most common urinary complications are ureteral stricture or obstruction, difficult catheterization, and pyelonephritis (Angioli, 1998; Goldberg, 2006). The gastrointestinal complication rate attributed to the Miami pouch is less than 10 percent and includes fistulas (Mirhashemi, 2004).

43-8 VAGINAL RECONSTRUCTION

Patients undergoing exenterative surgery are typical candidates for creation of a new vagina. Other less common indications include congenital absence of the vagina, postirradiation stenosis, and total vaginectomy. There are innumerable ways to perform the procedure, and the type of reconstruction typically is determined by both the surgeon's personal experience and the woman's clinical circumstances.

Vaginal reconstruction at the time of exenteration is a very personal choice. Not every woman will desire a new vagina, and others will be unhappy with the functional result (Gleeson, 1994a). Reconstruction significantly prolongs an already lengthy operation and may lead to additional perioperative morbidity (Mirhashemi, 2002). However, proponents suggest that filling the large pelvic defect and bringing in a new source of blood supply may prevent postoperative fistula or abscess formation (Cain, 1989; Jurado, 2000).

Of the reconstruction choices, *pudendal thigh fasciocutaneous flaps* are technically easy to perform, but rates of sexual satisfaction are disappointingly low (Gleeson, 1994b). An omental flap with *split-thickness skin graft* (STSG) is another straightforward procedure with minimal morbidity (Kusiak, 1996). *Rectus abdominis myocutaneous* (RAM) *flaps* and *gracilis myocutaneous flaps* (GMC) are technically more challenging, take longer to perform, but demonstrate the most satisfying functional results (Lacey, 1988; Smith, 1998). Regardless of reconstruction technique, sexual adjustment is often significantly impaired in women after pelvic exenteration (Ratliff, 1996). Other techniques are used less commonly and will not be covered in this section.

Preoperative

PATIENT EVALUATION

The surgeon should have an open discussion with the patient about the risks and benefits of vaginal reconstruction. Some women may have unrealistic expectations that are important to address preoperatively. Others may not wish to incur additional morbidity. The patient also should be aware that intraoperative complications may dictate a change of plans and the need to abort reconstruction.

CONSENT

Patients who are motivated to undergo creation of a new vagina must be counseled very carefully. Postoperative patient concerns are expected and include self-consciousness about being seen in the nude by their partner, vaginal dryness, and vaginal discharge (Ratliff, 1996). The potential morbidity of the neovagina depends on the type of reconstruction. Flap necrosis, prolapse, wound separation, or other complications may require re-operation or lead to an unsatisfying end result or both.

PATIENT PREPARATION

The preceding exenterative surgery typically dictates preoperative preparation. Modifications may be required depending on the type of neovaginal reconstruction. For example, the legs may need to be surgically prepared beyond the knees (gracilis flap), or a suitable donor site may need to be identified (STSG).

Intraoperative

Surgical Steps

1. **Pudendal Thigh Fasciocutaneous Flap.** From a perineal approach, the planned incisions are marked along the skin from the non-hair-bearing areas just lateral to the labia majora. Flaps should be roughly 15 × 6 cm. The most inferior skin margin should be level with the lower part of the gaping perineal defect. The skin incision is begun at the superior flap margin and dissected to include the underlying subcutaneous tissue and fascia lata (Fig. 48-8.1). The posterior labial artery, which is a branch of the internal pudendal artery, provides blood supply.

   The flap's edges are approximated in a running subcuticular suture line with 4-0 delayed-absorbable suture. The neovagina is

inserted into the perineal defect, and the incision sites are closed with interrupted stitches of 3-0 delayed-absorbable suture. Bilateral Jackson-Pratt (JP) drains have been placed beneath the harvest sites to prevent seroma formation. The perineal defect also generally requires some suturing for closure (Fig. 48-8.2). The apex of the neovagina then may be sutured abdominally to the hollow of the sacrum and covered with an omental J-flap to provide additional neovascularization.

FIGURE 43-8.1

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Raising the perineal flaps.

FIGURE 43-8.2

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

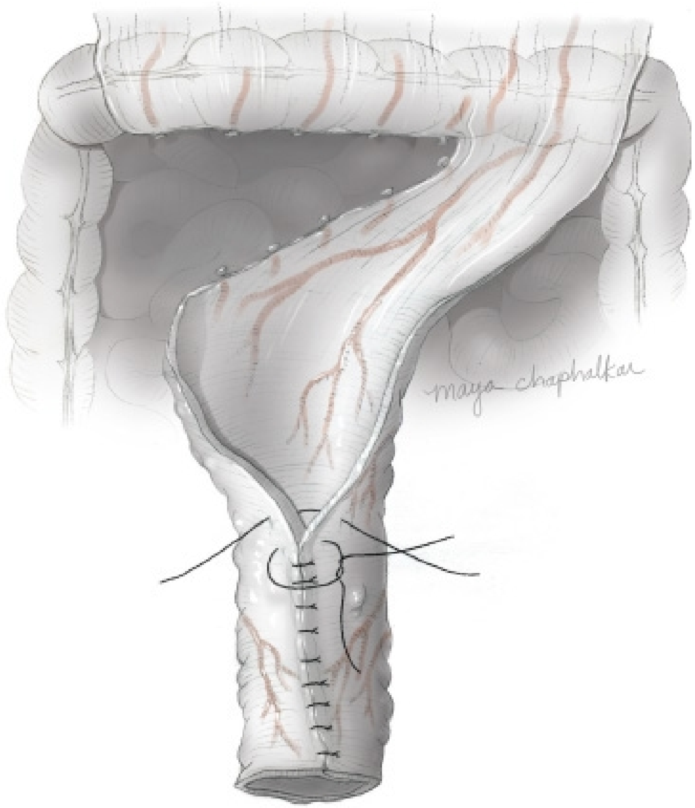
Perineal flap closure.

2. **Omental J-Flap with Split-Thickness Skin Graft.** Modification of the omental flap, which normally is used to close off the pelvic inlet after exenteration, can create a cylinder providing anterior, posterior, and lateral walls for a new vagina.

   From an abdominal approach, the omentum is detached from the stomach with a ligate-divide-staple (LDS) device, usually from right to left, until it will comfortably reach the pelvis as a J-flap (see Section 43-12, Omentectomy). Only three quarters of the omentum is divided to preserve the left gastroepiploic artery. The distal omentum is rolled into a cylinder and sutured together with interrupted stitches of 3-0 gauge delayed-absorbable suture (Fig. 43-8.3). The proximal end can be closed with interrupted sutures or a TA stapler. The omental cylinder then is sutured to the vaginal introitus.

   The STSG is harvested from the donor site and sutured over a vaginal mold with 4-0 delayed-absorbable suture (see Fig. 41-12.1). From a perineal approach, the mold is placed into the neovaginal space and sutured into place at the introitus (Fig. 43-8.4). The STSG skin harvest sites are covered with a Tegoderm dressing.

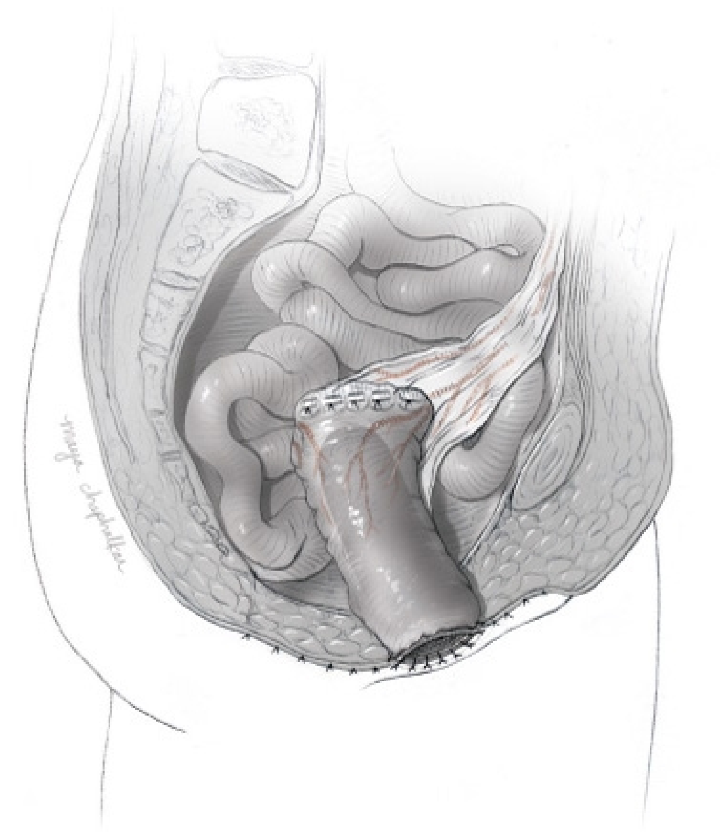
FIGURE 43-8.3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Raising the omental J-flap.

FIGURE 43-8.4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

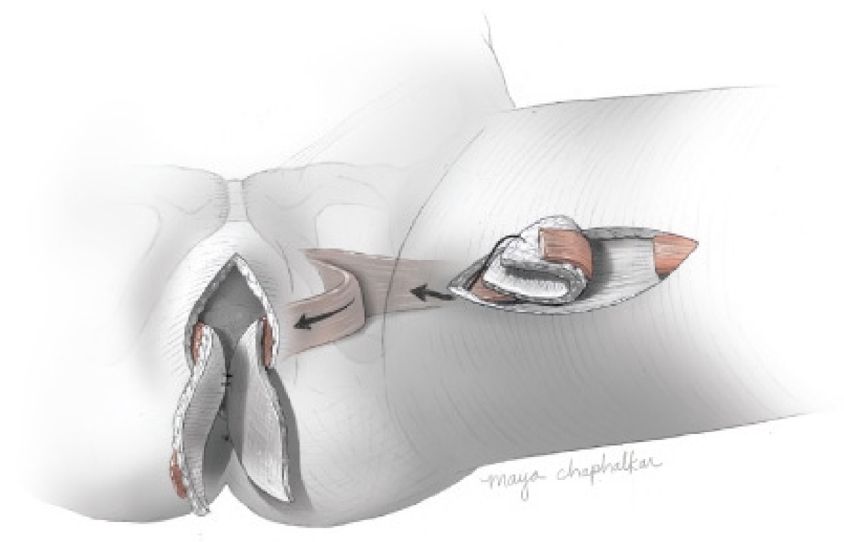
Insertion of the split-thickness skin graft (STSG).

3. **Gracilis Myocutaneous Flap.** From a perineal approach, a reference line is drawn on the medial thigh from the pubic tubercle to the medial tibial plateau. This line follows the adductor longus muscle. Posterior to this line, an island of skin, its associated subcutaneous tissue, and the gracilis muscle will serve as the flap (Fig. 43-8.5). The planned elliptic incision is marked, and a full-thickness skin incision through the reference line is continued through the subcutaneous fat and the fascia lata. The belly of the gracilis muscle is isolated at its distal margin and divided. The remainder of the incision is completed around the marked skin island margin. The gracilis is mobilized fully with blunt and sharp dissection from distal to proximal. This preserves the dominant vascular pedicleâ€”a branch of the medial femoral circumflex artery. This vessel enters the deep anterior belly of the muscle about 6 to 8 cm from the pubic tubercle.

   Through the operative site, a subfacial tunnel is bluntly developed medially to the open perineal defect. The left gracilis muscle flap is rotated clockwise against the thigh, i.e., rotated first posteriorly and then medially. It is placed through the tunnel and allowed to hang freely between the patient's legs. The right flap is rotated counterclockwise and similarly positioned.

   Beginning at the distal tip, the tubular gracilis neovagina is constructed by suturing the skin edges of the right and left skin islands together with interrupted stitches using 4-0 delayed-absorbable suture. The proximal opening should accommodate two or three fingers. The neovagina is rotated cephalad into the pelvis and anchored posteriorly to the levator plate abdominally. This suturing prevents prolapse. Redundant flap skin is trimmed, and the proximal skin is sutured to the introitus with interrupted stitches of 3-0 delayed-absorbable suture. The graft harvest incision sites are closed with interrupted stitches of 3-0 delayed-absorbable suture.

FIGURE 43-8.5



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Gracilis myocutaneous (GMC) flap.

4. **Rectus Abdominis Muscle Flap.** A skin island can be harvested from any location on the abdominal wall as long as its base is at the umbilicus. Typically, a 10 × 15 cm skin island is marked, and at its superior border, the skin, subcutaneous tissue, and anterior rectus sheath are incised. One belly of the rectus abdominis muscle is freed with blunt dissection from the posterior sheath (Fig. 43-8.6). The belly is divided proximally, and anastomotic vessels connecting to the superior epigastric system are ligated.

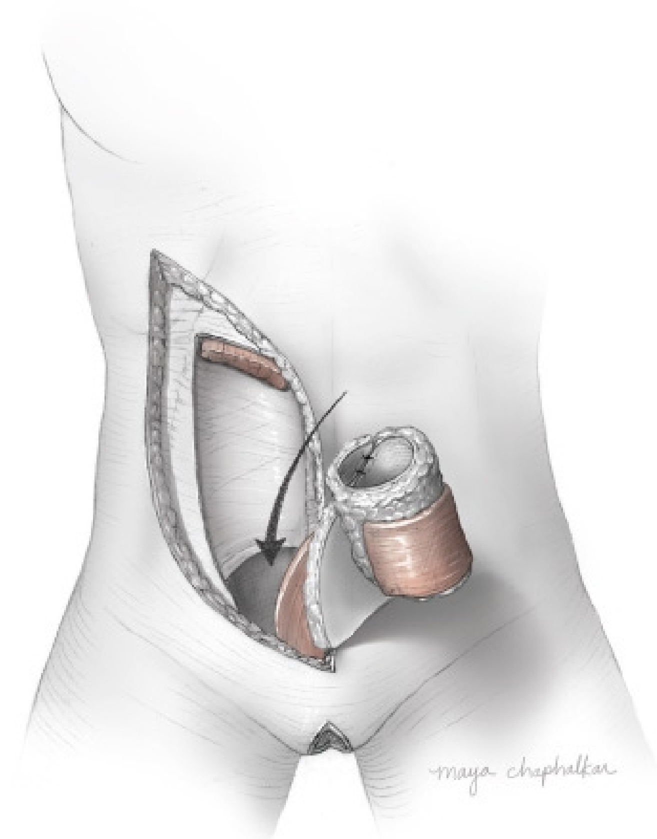
   The remaining borders of the skin island are incised through the anterior rectus sheath to the arcuate line, and the subcutaneous fat is mobilized along the lateral and medial margins of the rectus muscle belly. The rectus muscle then is dissected bluntly from the posterior sheath to raise the flap. The peritoneum is cut inferiorly, beginning at the arcuate line and extending the full length of the midline incision well beyond the flap. The rectus muscle then is dissected bluntly inferiorly from the anterior sheath to its insertion onto the pubic bone. The inferior rectus flap then can be rotated posteriorly into the pelvis.

   The flap is coiled around a syringe to form a tube (Fig. 43-8.6). The skin edges are approximated with 4-0 delayed-absorbable suture. The syringe is removed, and the tube is placed into the pelvis. The pelvic end is closed. The RAM flap must be put into the pelvis without tension to prevent occlusion of the dominant vascular supply from the inferior epigastric artery.

   The open end of the neovagina is brought out under the pubic symphysis to the perineum, where it is attached to the vulvar defect using interrupted vertical mattress stitches using delayed-absorbable suture. An omental J-flap also may be prepared to provide additional blood supply.

   Typically the abdominal wall defect can be closed primarily. The ipsilateral adjacent skin should first be undermined. Next, the operating table can be partially flexed to reduce tension on the closure. The posterior sheath is brought toward the midline and closed by running a monofilament permanent suture. The anterior rectus sheath does not necessarily require separate closure, but if desired, a defect can be covered with mesh placement. After closing the fascia, a JP suction drain is inserted in the wound site before completing the skin closure with staples.

FIGURE 43-8.6



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Rectus abdominis myocutaneous (RAM) flap.

Postoperative

The presence of a vagina significantly improves a woman's quality of life and reduces sexual problems after exenteration (Hawighorst-Knapstein, 1997). Vaginal reconstruction may be beneficial to a patient's self-image. The knowledge that intercourse is possible may be reassuring even if she chooses not to be sexually active postoperatively. Morbidity from the procedure largely depends on the type of neovagina.

Pudendal thigh flaps are the easiest to perform but perhaps also the most likely to be nonfunctional. Long-term sequelae may include vulvar pain, chronic vaginal discharge, hair growth, and protrusion of the flaps. These symptoms may discourage patients and their partners from attempting sexual activity (Gleeson, 1994b).

Omental flap/STSG neovaginas may become infected at the donor or recipient site. Sloughing is a common complication, especially in previously irradiated patients. In addition, stenosis may develop unless dilators are used postoperatively or sexual intercourse is regular.

Gracilis myocutaneous flaps may be difficult to pass into the pelvis during the procedure and have the potential for partial or complete tissue loss owing to necrosis from an inherently tenuous blood supply (Cain, 1989). Flap loss is significantly more common with rectosigmoid anastomosis during exenteration (Soper, 1995). Long term, prolapse is another relatively common problem. Residual scarring on the legs is a common, albeit relatively minor, complaint postoperatively.

Rectus abdominis muscle flaps are perhaps the best choice for vaginal reconstruction at the time of pelvic exenteration. Ideally, they fill pelvic dead space, reduce the risk of fistulas, and provide fulfilling sexual activity (Goldberg, 2006). However, the donor site may be difficult to close primarily or lead to a postoperative hernia or dehiscence. The operating time is also increased because two surgical teams are not possible. Flap necrosis, fistula, and vaginal stricture or stenosis are other frequent complications (Soper, 2005).

43-9 PELVIC LYMPHADENECTOMY

Pelvic lymph node removal of is one of the hallmarks of surgical staging and is commonly indicated for patients with uterine, ovarian, and cervical cancer. Pelvic lymphadenectomy implies a complete removal of all nodal tissue within an area bordered by well-defined anatomic landmarks. These include: midportion of the common iliac artery (proximally), circumflex iliac vein (distally), midportion of the psoas muscle (laterally), ureter (medially), and obturator nerve (posteriorly) (Whitney, 2005).

Additional definitions are used commonly in association with lymphadenectomy. For example, pelvic lymph node *sampling* is a more limited procedure within the same anatomic boundaries and is particularly intended to remove any enlarged or suspicious nodes (Whitney, 2005). Sampling has some valid indications depending on the clinical circumstances but is not a reliable method for accurately excluding nodal metastases (Carnino, 1997). Pelvic lymph node *dissection* is a vague term that may range from sampling to lymphadenectomy.

Removal of at least four lymph nodes from each side (right and left) is a minimum requirement to validate that an adequate lymphadenectomy has been performed (Whitney, 2005). Ideally, the procedure should yield more than 11 pelvic nodes from multiple sites (Cragun, 2005). However, removal of more lymph nodes increases the risk of postoperative complications (Franchi, 2001). In general, the extent of pelvic lymphadenectomy will depend on the clinical circumstances and will vary by clinician. Moreover, lymphadenectomy completeness is not only a reflection of total node counts but also depends on diagnostic skills of the interpreting pathologist.

Removal of enlarged pelvic nodes may be required to achieve optimal debulking of ovarian cancer. In addition, debulking of grossly involved pelvic lymph nodes also may confer a survival benefit in selected endometrial and cervical cancer patients (Havrilesky, 2005; Kupets, 2002). However, there is controversy as to whether systematic removal of pelvic nodes confers a true survival benefit or solely provides more accurate staging information in otherwise "understaged" patients (Panici, 2005).

Pelvic lymphadenectomy usually is an open procedure. The emerging laparoscopic approach has a learning curve to achieve adequate nodal counts (Kohler, 2004; Schlaerth, 2002). Extraperitoneal pelvic lymphadenectomy is performed even less commonly (Larciprete, 2006). Preoperative identification of suspicious nodes by lymphatic mapping and sentinel node identification remains an experimental strategy in gynecologic cancer surgical staging (Di Stefano, 2005; Levenback, 2002).

Preoperative

PATIENT EVALUATION

Imaging studies such as computed tomographic (CT) scanning and magnetic resonance (MR) imaging are commonly performed preoperatively in women undergoing cancer-related surgery. These studies may suggest the presence of pelvic lymphadenopathy and help to guide a surgeon to the most suspicious areas.

CONSENT

Pelvic lymphadenectomy should be a straightforward procedure with few complications, but acute hemorrhage, postoperative lymphocyst, and obturator nerve injury are possible (Bosze, 1993). Obesity, previous radiation, prior pelvic infections, prior abdominal surgery, and other factors causing retroperitoneal fibrosis can add difficulty to dissection. Most of these destroy tissue planes and can lead to an increased risk of complications.

PATIENT PREPARATION

Routine bowel preparation and antibiotic prophylaxis are not required for lymphadenectomy but may be indicated for other concurrent surgeries.

Intraoperative

Surgical Steps

1. **Anesthesia and Patient Positioning.** Lymphadenectomy may be performed under general or regional anesthesia with a patient in supine position. A Foley catheter is placed, and the abdomen is surgically prepared.

2. **Abdominal Entry.** A midline vertical or transverse abdominal incision that allows adequate visualization is appropriate for this procedure. Self-retaining retractors should be adjusted to expose the external iliac artery in its entirety.

3. **Abdominal Exploration.** Pelvic lymph nodes should be palpated routinely during initial abdominal exploration. Unexpected grossly positive nodes may indicate that a proposed operative plan should be revised or abandoned (e.g., radical hysterectomy for cervical cancer) (Whitney, 2000).

4. **Retroperitoneal Exploration.** The retroperitoneal space typically already has been entered through the round ligament during preceding surgical procedures. However, to improve visibility, a surgeon may further extend anterior and posterior broad ligament leaf openings.

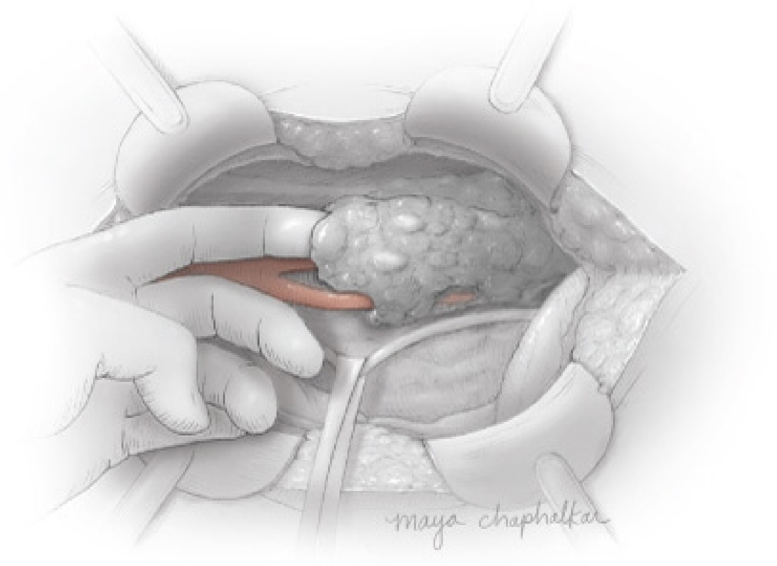
   Palpation of the external iliac artery pulsation just medial to the psoas major muscle should be the starting point, and its identification permits surgeons to locate relevant anatomy. Blunt dissection then is performed to visualize the bifurcation of the external and internal iliac arteries. The ureter is isolated, as described previously (see Section 43-1, Radical Abdominal Hysterectomy (Type III), Step 5). The remaining pelvic sidewall structures are covered with fatty lymphoid tissue and are not yet easily visible.

5. **Lateral Dissection.** An index finger is placed lateral to the bifurcation and used to bluntly dissect parallel to the external iliac artery along the psoas major muscle (Fig. 43-9.1). The general lack of arterial and venous branches along the external iliac vessels enables aggressive blunt dissection to be performed unless there is significant fibrosis. This maneuver separates the lateral preperitoneal fat from the medial fatty lymphoid tissue covering the vessels.

   Nodal tissue next is reflected medially to reveal the entire external iliac artery. Forceps traction and electrosurgical cutting typically are required to lift all adventitial tissue above the artery and maintain the correct plane of dissection. The circumflex iliac vein should be visible crossing over the distal external iliac artery before proceeding (see Fig. 43-9.3). The genitofemoral nerve should be visible parallel to the artery and overlying the psoas muscle.

   Bleeding is a common problem with pelvic lymphadenectomy that may be exacerbated by retroperitoneal fibrosis. Usually venous bleeding or avulsion of small vessel branches can be controlled quickly with vascular clips. Vascular anomalies are encountered regularly and may cause inadvertent hemorrhage if not identified.

FIGURE 43-9.1



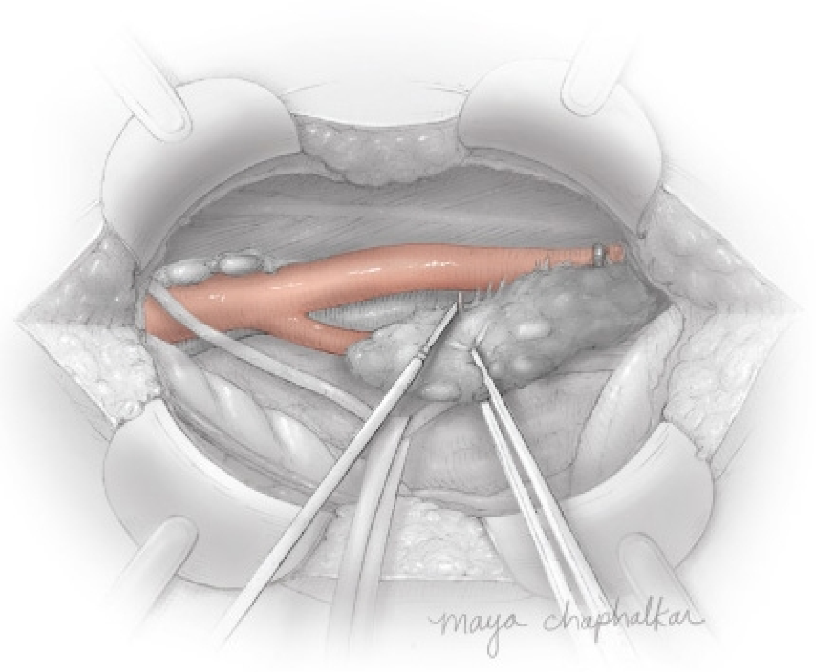
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Mobilizing the lateral nodal tissue.

6. **Removal of Distal Nodes.** A distal self-retaining retractor blade may need to be removed temporarily to resect all pelvic nodes heading toward the inguinal canal. The distal round ligament tie is elevated with one hand. The thumb of the other hand should be advanced directly beneath the round ligament and followed to the inguinal ring. Apposition of the tip of the thumb with the middle and adjoining fingertips will enable palpation, distal pinching, and removal of nodal tissue without cutting, clamping, or meaningful blood loss. The retractor blade then may be replaced.

7. **Dissection over the External Iliac Vein.** The ureter should be held medially on tension by Penrose drain to promote visualization of the pelvic sidewall. Forceps are used to place the nodal tissue bundle on medial traction. Alternating electrosurgical and blunt dissections are performed to reflect the nodal tissue medially until the external iliac vein is visualized (Fig. 43-9.2). The dissection is continued from proximal to distal above the internal iliac vessels. Nodal tissue may be transected with blunt and electrosurgical blade dissection along the inferomedial wall of the external iliac vein. The distal end of the bundle usually is tethered to the sidewall. Nodal tissue may be removed by placing a vascular clip and dividing the attachment. Additional fatty lymphoid tissue typically is seen within the anatomic boundaries. These nodes may be more adhered to the vessel and can be removed separately and added to the specimen.

FIGURE 43-9.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

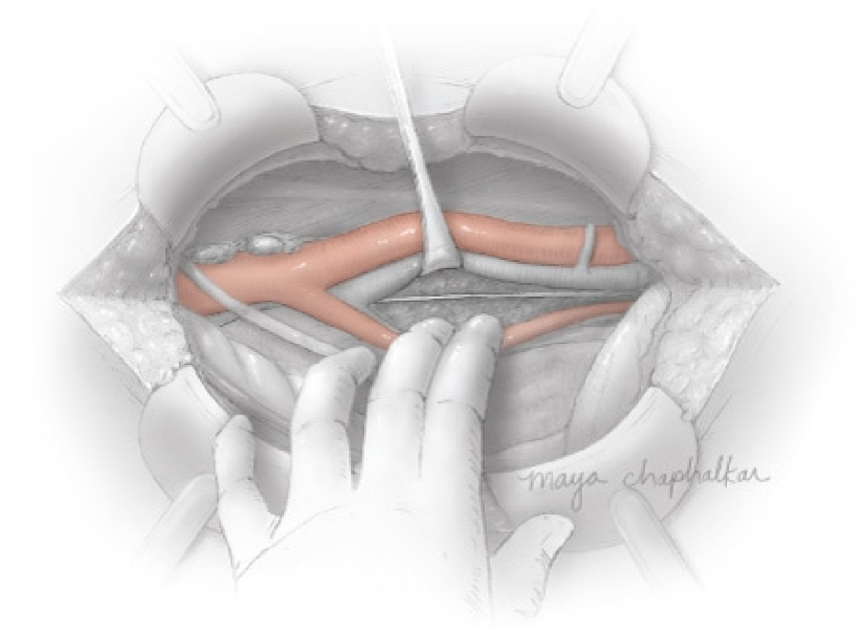
Medial dissection over the vein.

8. **Obturator Fossa Nodes.** The index finger is gently inserted between the psoas major muscle and the external iliac artery. Blunt dissection progresses downward to the obturator fossa. Lateral arterial or venous branches may need to be clipped and cut. Nodal tissue may be identified behind the external iliac vessels and added to the specimen.

   A vein retractor then is used to elevate the external iliac vein and expose the obturator fossa (Fig. 43-9.3). Debakey forcep tips can be used to mobilize nodal tissue inferiorly from the bottom of the vein. Accessory venous branches may be identified and clipped. The vein retractor then is removed and a hand inserted with the thumb directly beneath the vein. The tip of the thumb is advanced laterally, and the nodal bundle is scooped over the fingertips. This nodal packet may be removed by gently pinching along the pelvic sidewall.

   The obturator nerve may be palpable, and dissection purposely should remain superior. Firm fibrotic attachments may be dissected electrosurgically under direct visualization. The vein retractor is then reinserted, and the obturator nerve should be visible. Additional areas of fatty lymphoid tissue can be seen. Further blunt dissection is continued until the entire portion of the obturator fossa that lies anterior to the nerve is empty. Nodal tissue below the obturator nerve is not removed routinely because the obturator artery and vein traverse this area. Laceration of either of these vessels can result in retraction and catastrophic hemorrhage that is difficult to control.

FIGURE 43-9.3



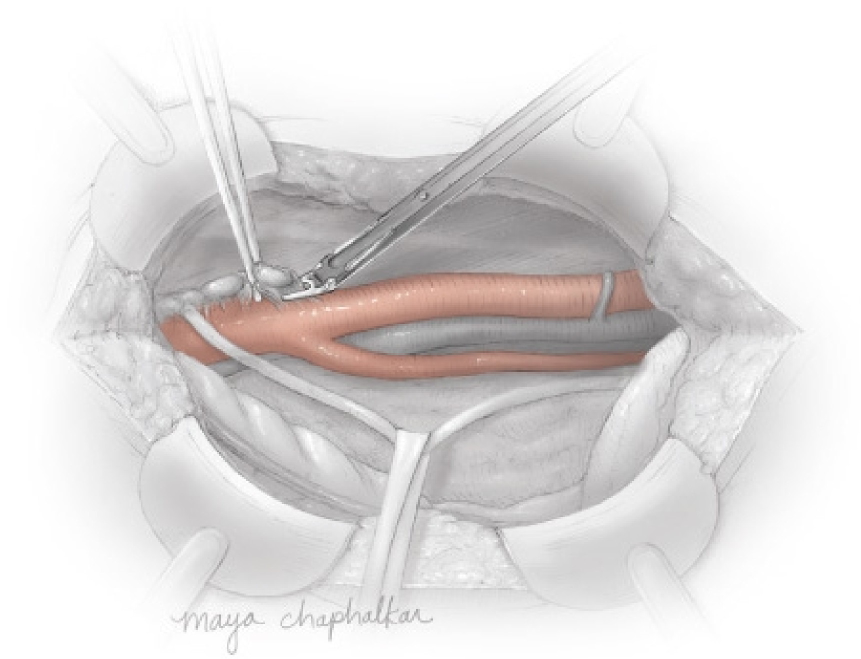
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Obturator fossa dissection.

9. **Distal Common Iliac Lymph Node Dissection.** The upper retractor blade is re-adjusted to allow increased visibility of the distal half of the common iliac artery. The colon may require mobilization using electrosurgical dissection along the white line of Toldt. Bowel then can be retracted sufficiently to allow access to the common iliac nodes.

   The lateral fatty lymphoid tissue may be removed by first grasping it with Debakey forceps and using electrosurgical dissection to establish a plane. Blunt dissection then may be performed in a proximal direction to further separate the nodal tissue from the artery. Electrosurgical coagulation or clips then may be used to detach the nodes (Fig. 43-9.4). Caution should be used on the right side because of the proximity of the underlying external iliac and common iliac veins and inferior vena cava (IVC). During lymphadenectomy, small veins that enter the anterior surface of IVC may be avulsed.

FIGURE 43-9.4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Distal common iliac dissection.

10. **Final Steps.** Gauze sponges may be opened and tightly placed into the obturator fossa and medial to the external iliac vein to tamponade any surface oozing while additional procedures are performed. There is no benefit to closing the retroperitoneal space or routinely using pelvic suction drainage (Bafna, 2001; Lopes, 1995; Suzuki, 1998).

Postoperative

Surgical blunt dissection techniques decrease the risk of inadvertent vessel or nerve injury but may increase the chance of postoperative lymphocyst formation. Also known as *lymphocoele,* these cysts usually are asymptomatic, transient collections of lymph with a thick fibrotic wall. Symptomatic or large lymphocysts usually will respond to percutaneous aspiration with or without drainage catheter placement (Mann, 1989). Sclerosis is uncommonly required. Laparotomy with marsupialization should be considered a last option (Liu, 2005). Omentoplasty may reduce the incidence of these complications but is not usually performed (Fujiwara, 2003).

Contusion is the most common type of obturator nerve injury. This functional complication may be indicated by motor or sensory changes as described in Chapter 40, Obturator Nerve Injury and typically resolves with time. However, transection of the obturator nerve should be immediately noted intraoperatively and an epineural repair performed (Vasilev, 1994).

43-10 PARA-AORTIC LYMPHADENECTOMY

Para-aortic lymphadenectomy implies a complete removal of all nodal tissue from within an area with well-defined anatomic boundaries. These include the inferior mesenteric artery (proximally), middle common iliac artery (distally), ureter (laterally), and aorta (medial) (see Fig. 38-15). The completeness of the procedure will vary by clinician, but an adequate dissection requires that lymphatic tissue at least be demonstrated pathologically from both the right and left sides (Whitney, 2005).

Removal of para-aortic lymph nodes is indicated routinely to surgically stage women with uterine and ovarian cancer because of their unpredictable patterns of lymphatic dissemination (Burke, 1996; Negishi, 2004). Moreover, removal of enlarged para-aortic nodes may be required to achieve optimal debulking of ovarian cancer and also may confer a survival benefit in selected endometrial and cervical cancer patients (Cosin, 1998; Havrilesky, 2005).

Para-aortic lymphadenectomy usually is an open procedure. Transperitoneal laparoscopic approach is available, although adequate nodal counts depend in large part on operator laparoscopic skills (Kohler, 2004).

Preoperative

PATIENT EVALUATION

Imaging studies such as computed tomographic (CT) scanning and magnetic resonance (MR) imaging may suggest the presence of para-aortic lymphadenopathy but are not completely accurate. For example, occult macroscopically positive para-aortic nodes are encountered commonly during ovarian cancer debulking (Eisenkop, 2001). Preoperative tests may help to guide a surgeon to the most suspicious areas but are not mandatory in most circumstances.

CONSENT

Para-aortic lymphadenectomy is not performed routinely worldwide because of the procedure's difficulty and potential for complications (Fujita, 2005). Of these, acute hemorrhage and postoperative ileus are associated most commonly. Other complications should be infrequent. However, in an obese woman, visibility in the area of dissection is decreased, and thus, the complexity of performing this delicate procedure is increased. The operative time is also lengthened considerably.

PATIENT PREPARATION

Routine bowel preparation and antibiotic prophylaxis typically are not required. However, other concurrent surgeries may dictate their use.

Intraoperative

Surgical Steps

1. **Anesthesia and Patient Positioning.** Lymphadenectomy may be performed under general or regional anesthesia with the patient in supine position. A Foley catheter is placed, and the abdomen is surgically prepared.

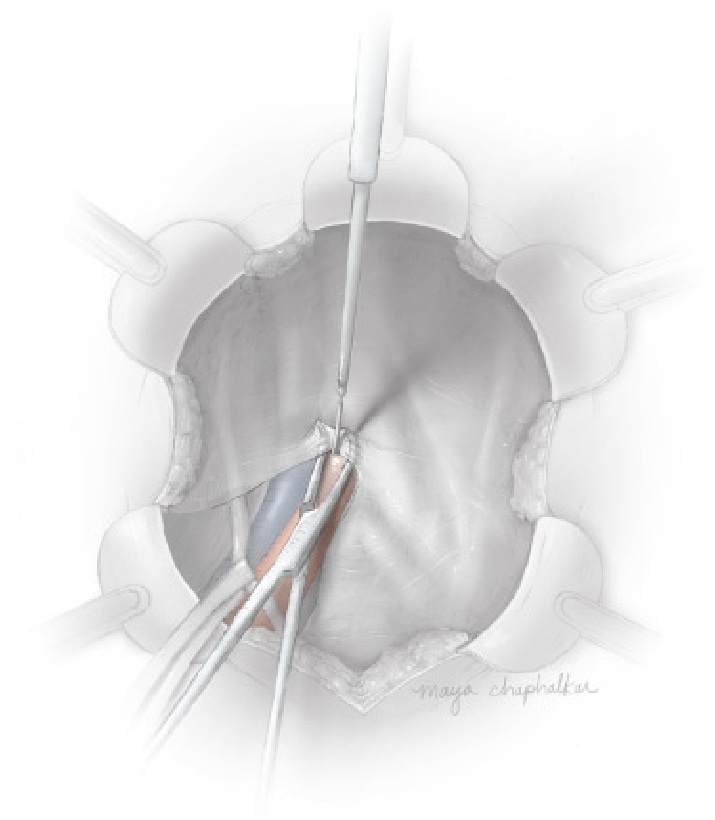
2. **Abdominal Entry.** A midline vertical abdominal incision that extends around and above the umbilicus provides optimal exposure. Alternatively, para-aortic lymphadenectomy also can be performed via a Cherney or a Maylard incision (see Sections 41-3, Cherney Incision and 41-4, Maylard Incision) (Helmkamp, 1990). A Pfannenstiel incision, in contrast, provides limited exposure and may not allow sufficient abdominal access if bleeding develops (Horowitz, 2003).

3. **Abdominal Exploration.** Para-aortic lymph nodes should be palpated routinely during initial abdominal exploration. A hand is placed beneath the small bowel mesentery to palpate the aorta. The index and middle fingers then are used to straddle the aorta and palpate for lymphadenopathy. Suspicious or grossly positive para-aortic nodes typically should be removed as one of the initial steps in the abdominal operation. Unexpected positive nodes may indicate that the proposed operative plan should be abandoned or revised (Whitney, 2000). For the majority of instances when no adenopathy is present, the dissection usually should be performed last because of the possibility of triggering catastrophic bleeding that otherwise might limit further surgery.

4. **Visualization.** Exposure and proper retractor positioning are perhaps the most important parts of the procedure. Thus, a self-retaining retractor is positioned to allow access to the aorta. The sigmoid colon should be gently retracted in a lower left direction, whereas small bowel and transverse colon are packed with laparotomy sponges into the upper abdomen. Modified Trendelenburg patient positioning is also helpful to shift bowel from the operative field. Additional sharp dissection along the right paracolic gutter may be necessary to sufficiently mobilize and move the cecum from the dissection plane. Once bowel has been cleared from the field, the peritoneum overlying the aorta and right common iliac artery should be visible. Both vessels should be palpated before proceeding.

5. **Opening the Retroperitoneal Space.** As described in Section 43-1, Radical Abdominal Hysterectomy (Type III), Step 5, the ureter is isolated and held laterally on a Penrose drain. A right-angle clamp is used to guide electrosurgical blade dissection of the posterior peritoneum in a medial direction over the right common iliac artery and aorta (Fig. 43-10.1). Staying directly above these arteries is a safe location because no vital structures cross these vessels medial to the ureter. The surgeon stops intermittently to palpate the course of the artery before continuing dissection in a cephalad direction to the inferior duodenal fold. Blunt dissection is performed to mobilize the duodenum, and the cephalad self-retaining retractor blade is repositioned to retract this bowel.

FIGURE 43-10.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Opening the retroperitoneal space.

6. **Exposing the Aorta and Inferior Vena Cava.** The surgeon returns to the area near the right ureter, where the posterior peritoneal dissection began. Electrosurgical cutting is used to incise the areolar sheath on top of the right common iliac artery, and dissection is continued proximally past the aortic bifurcation to the inferior mesenteric artery (IMA). Small perforating vessels may be encountered and coagulated.

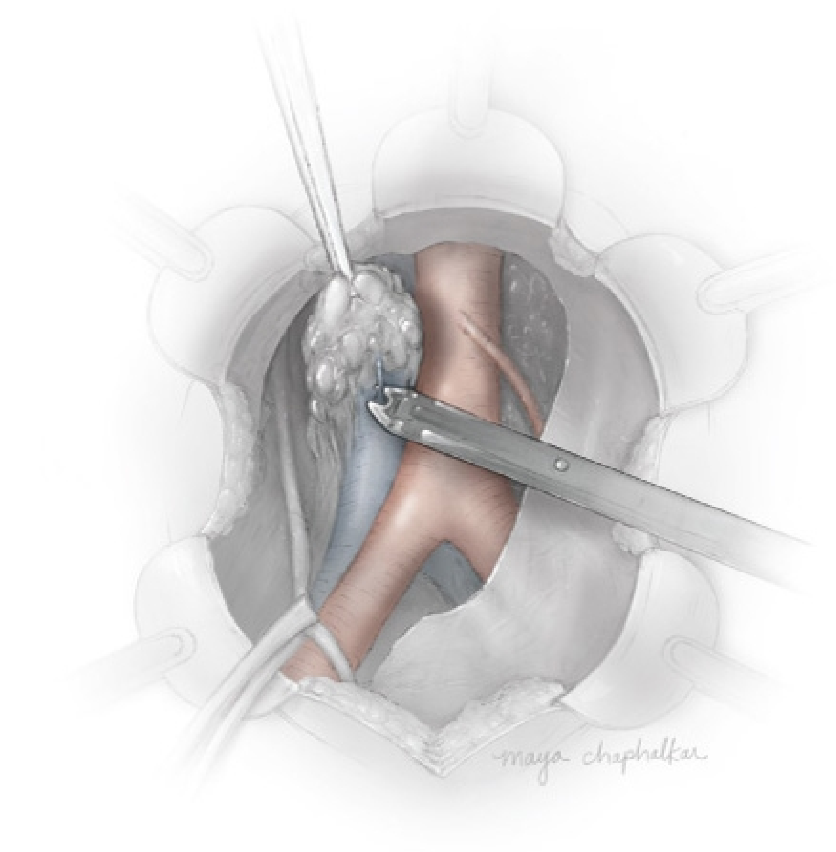
7. **Removal of Right Para-aortic Nodes.** Lymphadenectomy begins lateral to the midportion of the right common iliac artery. The ureter is held medially by traction on the Penrose drain while the nodal bundle is elevated with forceps and blunt dissection is performed to better visualize its fibrinous attachments to the distal artery.

   A right-angle clamp is placed under these fibers, and electrosurgical cutting is used to divide them. Blunt dissection will

demonstrate the right common iliac vein as it crosses beneath the artery. The adventitial sheath surrounding the common iliac vein is incised and extended upward by following the arterial direction to the level of the IMA. The lateral border of dissection is established by holding the ureter laterally and bluntly separating the lateral side of the inferior vena cava (IVC) from the retroperitoneal fat. The upper right abdominal retractor blade may need to be repositioned to improve visibility.

At this point, the right para-aortic node bundle has been largely detached medially, distally, and laterally. Lymph nodes are grasped distally with Debakey forceps and elevated to identify perforating veins from the IVC as gentle blunt dissection is performed in a proximal direction. The delicate nature of arterial and venous branches along the aorta and IVC warrant meticulous dissection to reduce bleeding. The "fellow's vein" is encountered routinely near the level of the aortic bifurcation and should be occluded with a vascular clip for hemostasis (Fig. 43-10.2). The nodal bundle can be removed by placing large vascular clips across the proximal end and transecting it.

FIGURE 43-10.2

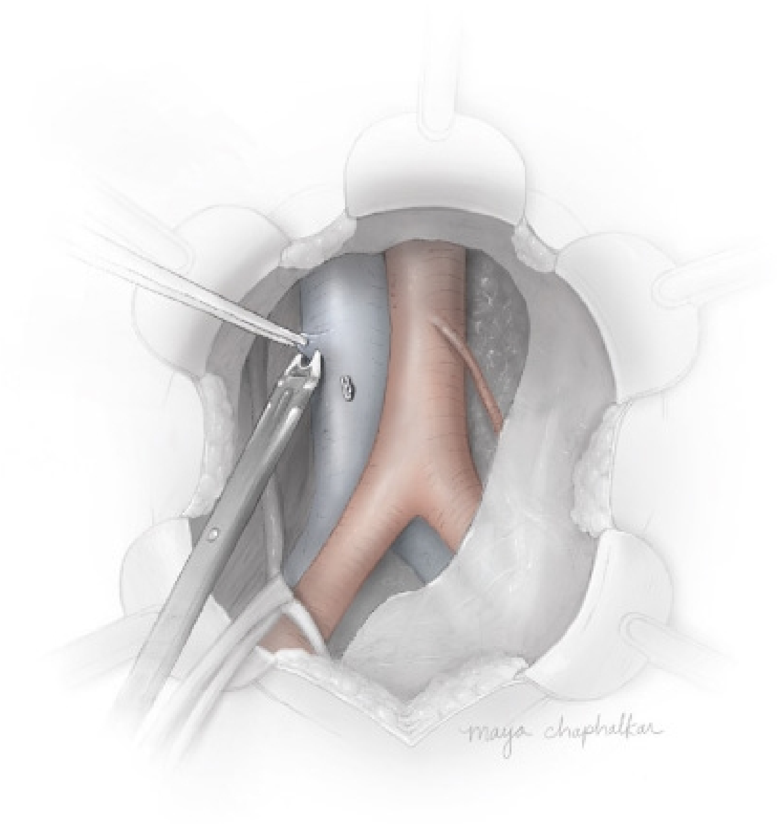


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Removal of right para-aortic nodes.

8. **Repair of Venous Bleeding.** The surgeon should prepare for small lacerations in the wall of the IVC or common iliac veins by inadvertent avulsion of perforating venous tributaries. Hemorrhage may be copious and immediate. Initially, pressure is applied with a sponge stick or finger. Second, exposure is assessed. Blood is suctioned from the abdominal cavity, retractors are repositioned, and incisions are extended if necessary. Lastly, proper vascular instruments are obtained. Venous bleeding usually can be repaired simply with vascular clips (Fig. 43-10.3).

FIGURE 43-10.3



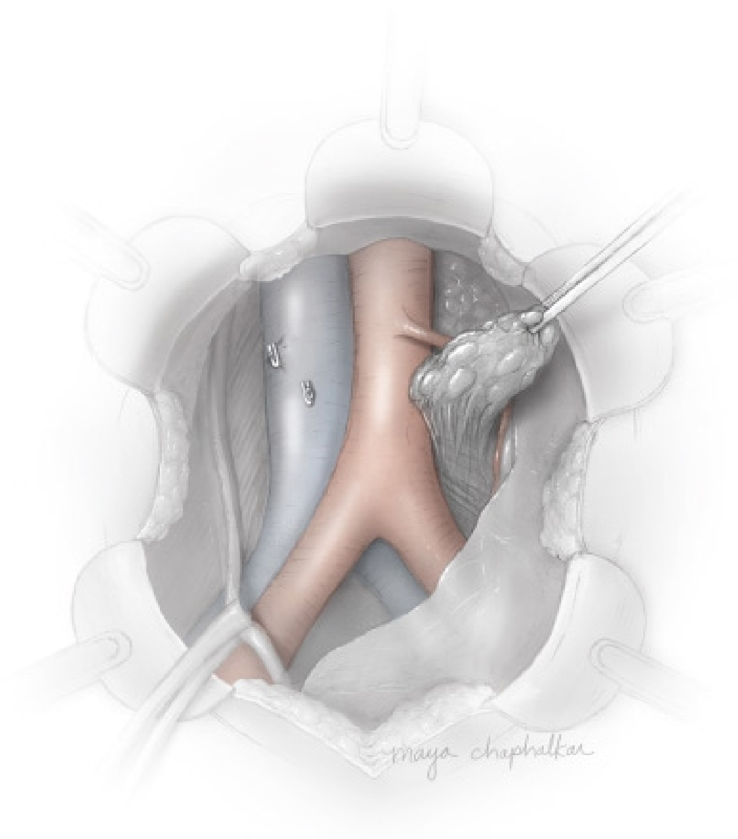
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Repair of venous bleeding.

9. **Removal of Left Para-aortic Nodes.** The upper left abdominal retractor blade is repositioned under the posterior peritoneal edge to access the left side of the aorta. Electrosurgical dissection is performed to incise the adventitial sheath of the aorta distally to the midportion of the left common iliac artery. Lateral blunt dissection at the level of the bifurcation should demonstrate the left ureter and establish this lateral boundary. Blunt posterior dissection is performed directly adjacent to the left side of the aorta to develop the medial plane between the nodal bundle and aorta. This dissection is continued to the vertebral bodies and then extended distally to the midportion of the left common iliac artery.

   The nodal bundle is held on traction to aid vascular clip placement and distal transection unless already freed by proximal dissection during a preceding pelvic lymphadenectomy. Nodal tissue is elevated and progressively lifted proximally while alternating blunt and electrosurgical dissection is performed to divide any remaining posterior attachments (Fig. 43-10.4). The dissection is continued cephalad to the IMA, where the nodal bundle is clipped and transected.

FIGURE 43-10.4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Removal of left para-aortic nodes.

10. **Removal of Interiliac Nodes.** Optionally, several additional lymph nodes may be removed by excising the fatty interiliac tissue. The posterior peritoneum at the aortic bifurcation is grasped, and electrosurgical dissection is performed along the inner side of both common iliac arteries. The crossing left common iliac vein is visible directly beneath. Blunt dissection is performed along the surface of the vein because there are typically a few small perforating vessels. Electrosurgical dissection can be used from right to left after a triangle-shaped area of fatty lymphoid tissue has been mobilized between the common iliac arteries.

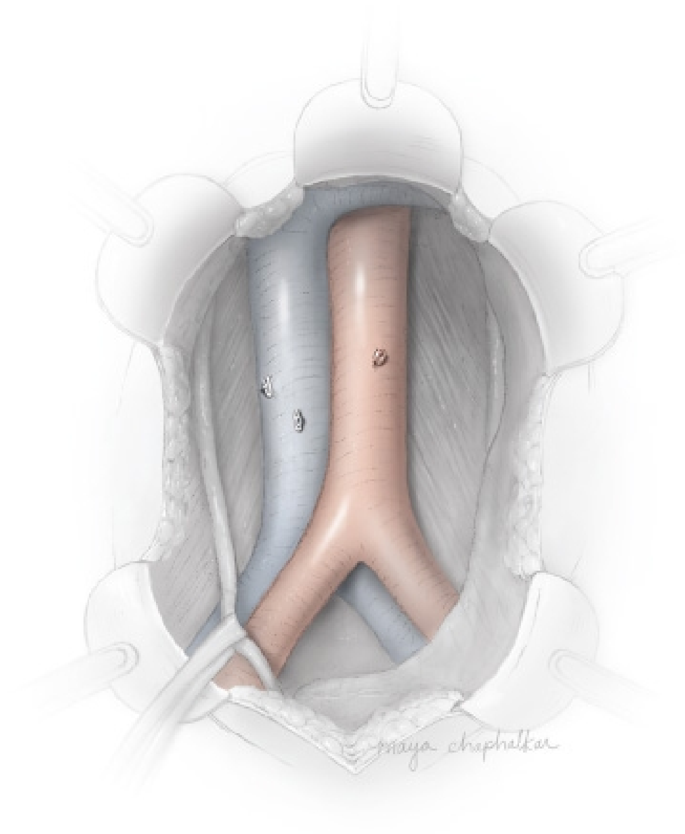
11. **High Para-aortic Lymphadenectomy.** Additionally, a surgeon may elect an extended dissection during ovarian cancer staging or when palpable lymphadenopathy is noted during uterine cancer surgery (Morice, 2003). The anatomic boundaries begin distally at the IMA and reach proximally to the entry level of the right ovarian vein and left renal vein (see Fig. 38-15). (Whitney, 2005).

    The midline peritoneal incision is incised more proximally, and the duodenal loop is dissected bluntly off the aorta and IVC. Repositioning of the retractor blade to retract this loop aids exposure. The right-sided para-aortic nodal bundle is regrasped with Debakey forceps, and dissection is continued proximally until the ovarian vein can be clipped and divided.

    Dissection of the left side begins with identification, clipping, and cutting of the IMA. This maneuver allows access to upper nodal tissue. The proximal boundary is established by blunt dissection to visualize the left renal vein. Removal of the left para-aortic nodes includes elevating the distal nodal bundle, performing blunt dissection to isolate and electrosurgically

coagulate lymphatic attachments, and progressing toward the renal vein, where the bundle is clipped and transected (Fig. 43-10.5).

FIGURE 43-10.5



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

High para-aortic lymphadenectomy.

12. **Retroaortic Lymphadenectomy.** This more extended dissection is optional and begins after left-sided para-aortic lymphadenectomy has been completed. The left-sided lumbar arteries can be visualized branching directly from the aorta. These vessels may be clipped and cut to allow manual rolling of the aorta from left to right and allow access to the retroaortic nodal chain. Typically, this procedure is performed when imaging studies have demonstrated suspicious nodes in the region.

13. **Final Steps.** Gauze sponges may be opened and gently placed in areas of nodal dissection to tamponade any surface oozing. There is no benefit to closing the retroperitoneal space or routinely using suction drainage (Morice, 2001).

Postoperative

The postoperative course following para-aortic lymphadenectomy in general follows that after laparotomy. However, the incidence of postoperative ileus is increased owing to longer operative time, increased bowel manipulation, extension of the incision, and additional blood loss. Most episodes will be mild, but longer hospital stays may be expected (Fujita, 2005).

43-11 EN BLOC PELVIC RESECTION

Ovarian cancer with contiguous encasement of the reproductive organs, pelvic peritoneum, cul-de-sac, and sigmoid colon is the main indication for en bloc pelvic resection, which is also known as *radical oophorectomy.* This effective technique aids a maximal cytoreductive surgical effort. As a result, removal of all microscopic and infiltrative peritoneal tumor in the pelvis has been associated with improved survival in women with advanced epithelial ovarian cancer (Aletti, 2006b). Moreover, pelvic recurrence rates are very lowâ€"reflecting the completeness of pelvic tumor eradication (Hertel, 2001). Many of the principles of en bloc pelvic resection mirror those of other procedures in gynecologic oncology.

Preoperative

PATIENT EVALUATION

Pelvic examination may show a relatively immobile mass, and abdominal-pelvic computed tomographic (CT) scanning typically demonstrates a pelvic mass and ascites. With the presumed diagnosis of advanced ovarian cancer, patients are prepared preoperatively for anticipated cytoreductive surgery. However, the need for en bloc resection usually is dictated by intraoperative findings rather than preoperative testing.

CONSENT

In general, women with advanced ovarian cancer undergoing cytoreductive surgery are at significant risk for complications, and they should be counseled accordingly. In one series of en bloc resections, 29 percent of patients required blood transfusion; 36 percent had minor postoperative complications such as incisional cellulitis, urinary tract infection, or ileus; and 13 percent had major postoperative complications such as pulmonary embolism, sepsis, or upper gastrointestinal hemorrhage (Bristow, 2003). Additional specific risks of en bloc resection that should be discussed include anastomotic leaks and fistulas (Park, 2006).

PATIENT PREPARATION

Primary anastomosis without colostomy is typical for most patients. Thus, bowel preparation is mandatory for any type of cytoreductive ovarian cancer surgery but particularly if en bloc pelvic resection is a possibility. One or more bowel resections may be required to achieve optimal debulking, and often, preoperative determination of the exact location of tumor infiltration is not easy. Pneumatic compression devices or subcutaneous heparin is particularly important due to the anticipated longer operation length and postoperative recovery (see Chap. 39, Prophylaxis Options). Moreover, patients should be typed and crossed routinely for packed red blood cell replacement.

Intraoperative

INSTRUMENTS

En bloc pelvic resection requires access to multiple sizes of bowel staplers, including gastrointestinal anastomosis (GIA), transverse anastomosis (TA), and end-to-end anastomosis (EEA) staplers. Additionally, a ligate-divide-staple (LDS) device may be used to divide vascular tissue pedicles.

Surgical Steps

1. **Anesthesia and Patient Positioning.** Bimanual examination under general anesthesia is especially important to confirm the necessity of leg positioning in Allen stirrups. Access to the perineum is crucial any time the EEA device may need to be placed in the rectum. Sterile preparation of the abdomen, perineum, and vagina is performed, and a Foley catheter is placed.

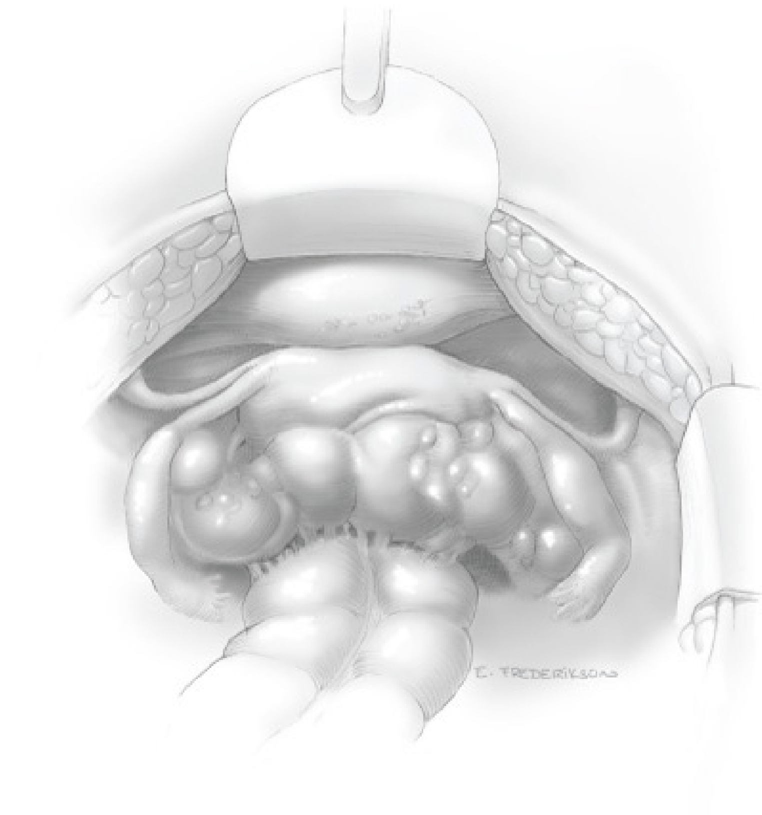
2. **Abdominal Entry.** Typically, a vertical incision is selected for ovarian cancer debulking surgery because the extent of disease cannot be known precisely beforehand. Debulking may require access to the diaphragm and other upper abdominal structures.

3. **Exploration.** The abdomen is explored thoroughly to first determine whether all gross disease can be removed safely. For example, unresectable upper abdominal tumor makes the prospect of a radical pelvic operation less attractive.

   Frequently during exploration, it is difficult to distinguish uterus, adnexa, and adjacent tumor. In Fig. 43-11.1, both ovaries

are grossly enlarged with tumor and are densely fixed into the posterior cul-de-sac with contiguous involvement of the uterus, rectosigmoid, and lateral sidewalls. Moreover, superficial implants coat the fallopian tubes, the vesicouterine fold, and much of the surrounding pelvic peritoneum. En bloc pelvic resection will allow removal of all gross disease.

FIGURE 43-11.1



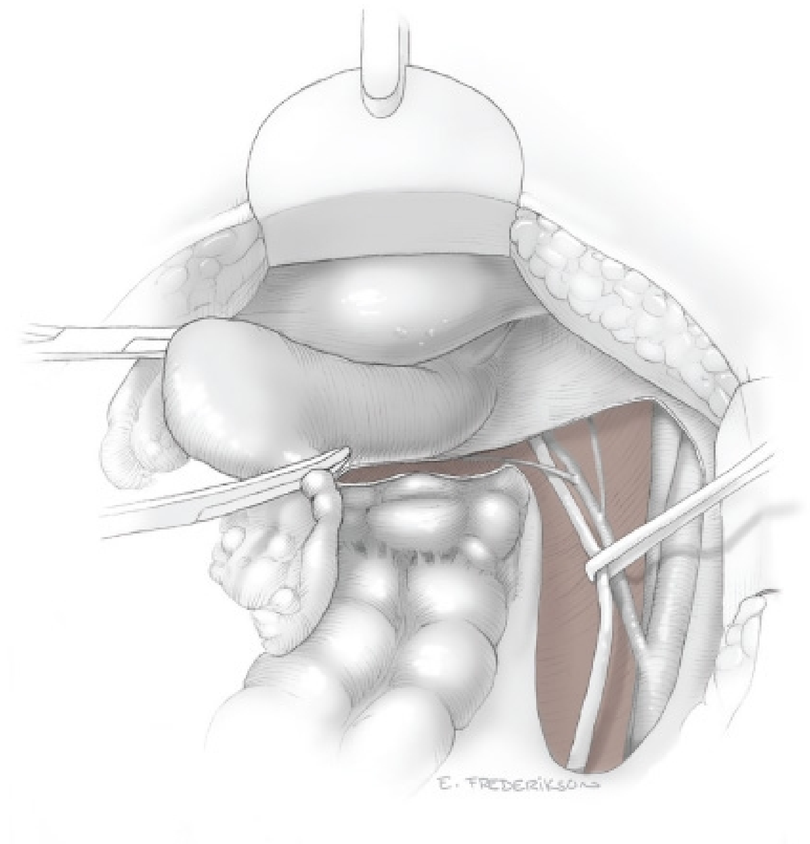
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Extensive ovarian cancer.

4. **Lateral Pelvic Dissection.** The lateral peritoneum is grasped with an Allis clamp, and an electrosurgical blade is used to enter the retroperitoneal space if the round ligaments cannot be located with certainty (Fig. 43-11.2). The loose areolar connective tissue of this space is dissected bluntly. The overlying peritoneum is incised sharply to create an opening in which the external iliac artery can be palpated. This artery is followed bluntly to the bifurcation with the internal iliac artery. The medial peritoneal leaf of the broad ligament is elevated to identify the ureter, around which a 1/4 -in Penrose drain is looped.

   The infundibulopelvic (IP) ligament typically will not be entirely distinguishable because of induration and anatomic distortion by tumor. A window is opened bluntly just superior to the ureter as it crosses above the pelvic brim to isolate a tissue pedicle that will include the IP ligament. The ligament is isolated, clamped, cut, and tied with 0-gauge delayed-absorbable suture before repeating the entire sequence on the contralateral side. The ureter then may be mobilized distally, and the anterior portion of the broad ligament is incised toward the vesicouterine fold using an electrosurgical blade. The round ligament will be identified during this dissection and divided separately.

FIGURE 43-11.2

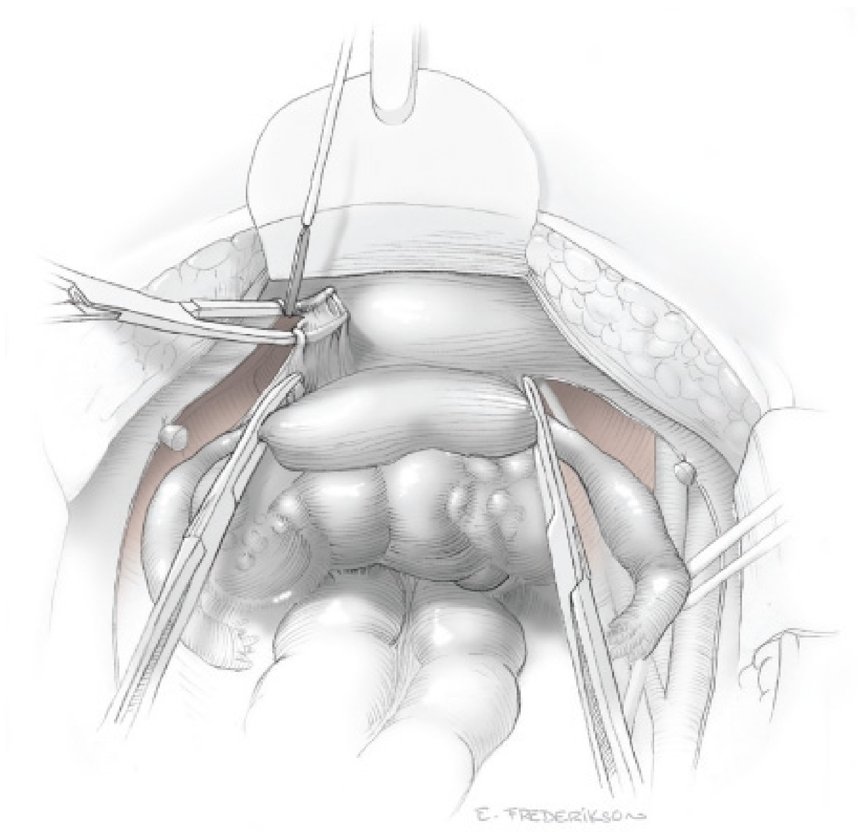


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Lateral pelvic dissection.

5. **Vesicouterine Dissection.** The anterior broad ligament dissection is continued with a right-angle clamp guiding the electrosurgical blade (Fig. 43-11.3). The peritoneum typically is edematous and thickened. En bloc removal of tumor implants within the vesicouterine fold will require a wide excision of the peritoneum over the dome of the bladder. Thus, the proximal end of the vesicouterine fold may be held on traction, and an electrosurgical blade may be used to dissect sharply in a caudal direction toward the cervix while encompassing the tumor. The bladder mucosa typically is not entered but may be simply repaired if an inadvertent cystotomy occurs (see Fig. 40-40). The whitish cervix will be seen, and the bladder then may be advanced distally in the usual manner. The ureters are held laterally while the uterine vessels are freed of surrounding connective tissue (skeletonized), clamped, cut, and ligated.

FIGURE 43-11.3

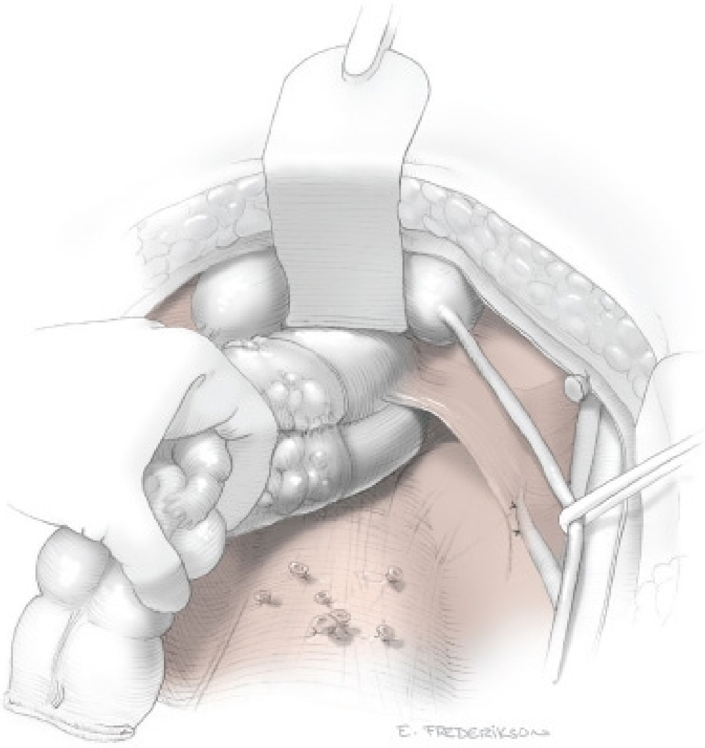


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Vesicouterine dissection.

6. **Dividing the Sigmoid.** The ureters are held laterally while a right-angle clamp guides electrosurgical blade dissection of the posterior peritoneum to the sigmoid mesentery. The sigmoid segment that lies proximal to the tumor is selected, and the underlying mesentery is incised superficially with an electrosurgical blade on each side. A GIA stapler is inserted to divide the bowel. The remaining mesentery is scored superficially with an electrosurgical blade and divided with the LDS (small pedicles) or clamps and ties (larger pedicles). The inferior mesenteric artery (IMA) branches are the largest vessels encountered. These are clamped, cut, and ligated separately. The avascular retrorectal space between the rectum and the sacrum then may be dissected bluntly to completely mobilize the rectosigmoid down to the cervix (Fig. 43-11.4).

FIGURE 43-11.4

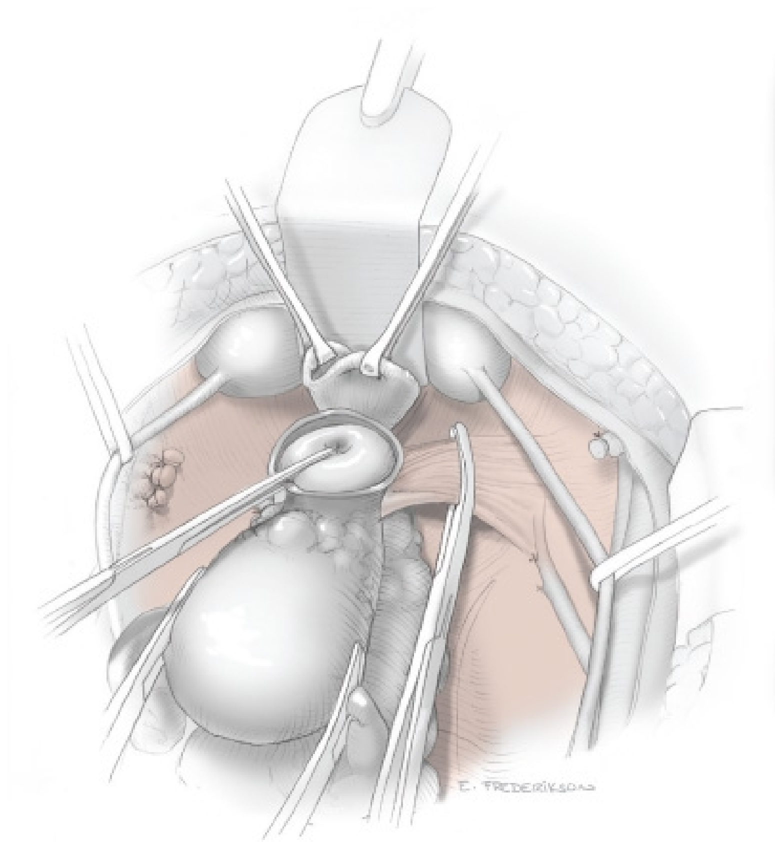


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Dividing the rectosigmoid.

7. **Retrograde Hysterectomy.** The bladder is advanced distally onto the upper vagina with sharp electrosurgical blade dissection. The distal anterior vaginal wall is grasped with a Kocher clamp. The anterior vaginal wall then is incised at 12 o'clock with an electrosurgical blade, and the incision is extended laterally to the right and left. The cervix is grasped with a Kocher clamp and retracted to expose the posterior vaginal wall. An electrosurgical blade is used to incise this wall transversely and enter the rectovaginal space. An Allis clamp is placed on the proximal edge of the anterior and posterior vagina to apply caudad traction and reduce bleeding. A retrorectal hand is placed to assess whether the tumor extends into the rectovaginal septum beyond the cervix. With large masses, distal dissection may be required into the rectovaginal septum to reach a point distal to the tumor's leading edge. Alternatively, smaller tumors may allow proximal dissection in the rectovaginal septum. This gains additional rectal length distal to the tumor and allows for creation of a higher anastomosis. Finally, the remaining uterosacral and cardinal ligaments are clamped in a retrograde fashion while confirming lateral ureteral positioning (Fig. 43-11.5).

FIGURE 43-11.5

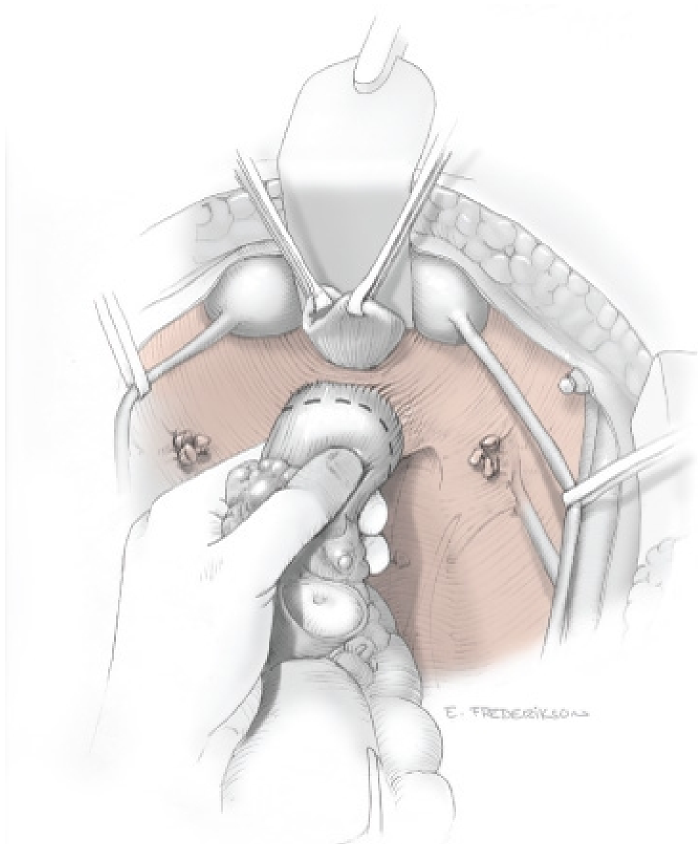


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Retrograde hysterectomy.

8. **Distal Rectal Division.** The mucosa of the rectal segment distal to the tumor is circumferentially dissected free of mesenteric attachments and rectal pillars by constant traction on the en bloc specimen (Fig. 43-11.6). The TA stapler is inserted into the pelvis and fired to transect the rectum and lift the uterus, adnexa, rectosigmoid, and surrounding peritoneum out of the pelvis. The vaginal opening then may be closed in a running fashion with 0-gauge delayed-absorbable suture (Fig. 43-11.7).

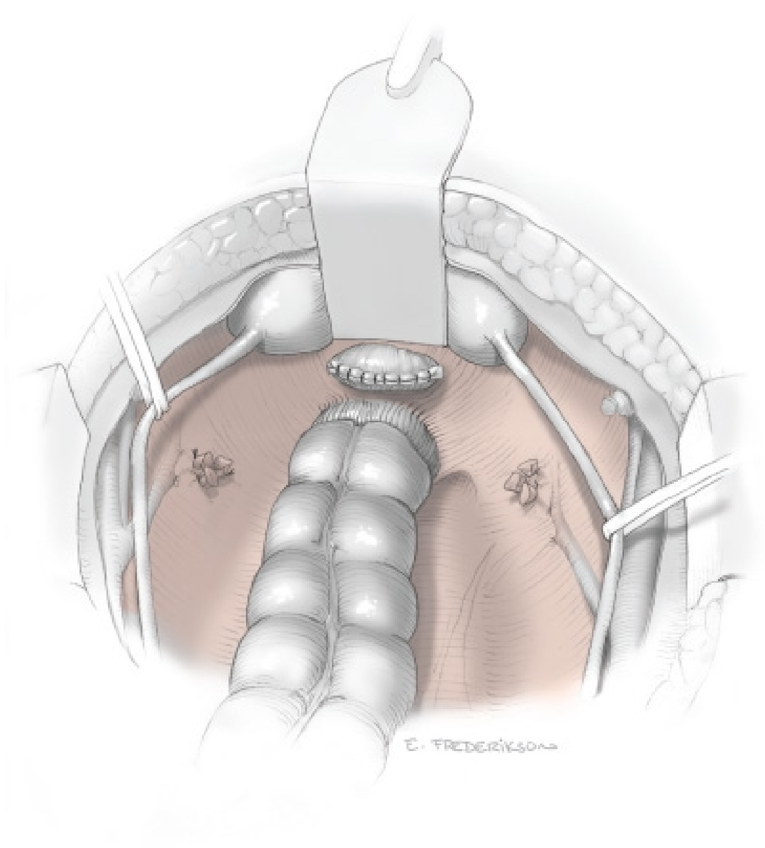
FIGURE 43-11.6



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Rectosigmoid resection.

FIGURE 43-11.7



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Final appearance.

9. **Final Steps.** The surgeon then will proceed with additional procedures if necessary to complete the ovarian cancer debulking surgery. A colostomy or rectosigmoid anastomosis may require mobilization of the splenic flexure and is performed near the end of surgery (see Sections 43-15, Colostomy and 43-19, Low Anterior Resection). Postoperative drains may be placed at the surgeon's discretion. Occasionally, the bladder also may require testing to exclude inadvertent injury during vesicouterine dissection. All pedicle sites should be rechecked for hemostasis.

Postoperative

En bloc pelvic resection of primary and recurrent ovarian cancer permits a high rate of complete debulking with acceptable morbidity and mortality rates (Park, 2006). Urinary tract infection, pneumonia, deep venous thrombosis, wound cellulitis, and postoperative ileus are relatively common events following major abdominal surgery for ovarian cancer. Reoperation for anastomotic breakdown or postoperative hemorrhage specific to en bloc pelvic resection should be uncommon (Bristow, 2003; Clayton, 2002).

43-12 OMENTECTOMY

The omentum typically is removed for two reasons: tumor debulking or cancer staging. Patients who present with advanced ovarian cancer almost invariably have metastases to the omentum. The extent of this "omental cake" often is difficult to appreciate on imaging studies, and a tumor may be massive and involve the upper gastrocolic ligament, anterior abdominal wall, splenic hilum,

and transverse colon (see Fig. 35-16). Thus, the surgeon should be prepared to encompass the entire tumor with an adequate resection.

Omentectomy is also indicated routinely for staging patients with ovarian cancer or with uterine papillary serous carcinoma who do not have obvious metastatic disease (Geisler, 1999). Infracolic (below the transverse colon) omentectomy is sufficient for most clinical circumstances, but supracolic (total) omentectomy may be indicated for a large omental cake.

Preoperative

PATIENT EVALUATION

Imaging studies may suggest the presence of an omental cake, but the extent is difficult to ascertain until exploration in the operating room.

CONSENT

Although bleeding may follow inadequate vessel ligation, complications from omentectomy are rare. Obesity and intra-abdominal adhesive disease, however, may increase these risks. Obesity results in a much thicker omentum and resulting thicker vascular pedicles that may slip from clamps or ligatures. Additionally, prior upper abdominal surgeryâ€”particularly gastric bypassâ€”may cause adhesions and a more difficult resection. In addition to these risks, women with an omental cake should be informed of a possible need for bowel resection, splenectomy, or other radical debulking procedure to remove an entire tumor.

PATIENT PREPARATION

Bowel preparation should be performed when an omental cake is present because of the possibility of colon resection. The risk of infection following omentectomy is low. However, this surgery typically is performed with other gynecologic procedures that warrant antibiotic prophylaxis.

Intraoperative

Surgical Steps

1. **Anesthesia and Patient Positioning.** Omentectomy typically is performed as an inpatient procedure under general anesthesia. The patient is positioned supine, a Foley catheter is placed, and the abdomen is surgically prepared.

2. **Abdominal Entry.** Infracolic omentectomy may be performed through any type of incision. However, because of the uncertain extent of disease that accompanies these cases, a midline vertical incision is selected most commonly.

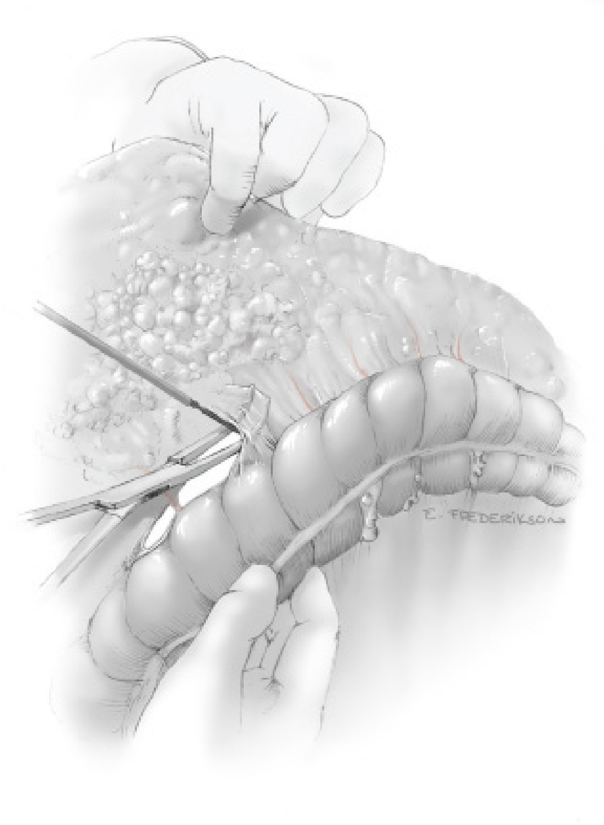
3. **Exploration.** Palpation of the omentum is often the first step in exploring the abdomen. This organ is directly beneath a midline vertical incision and should be readily visible. Omentectomy typically is the first procedure performed in women with an omental cake and presumed ovarian cancer. The omentum usually can be removed quickly and sent for frozen-section analysis while the surgeon places a self-retaining retractor and proceeds with the remaining planned operation.

4. **Visualization.** The surgeon gently grasps the infracolic omentum and pulls it out of the abdomen through the incision. The borders of any omental cake can be seen directly or palpated. The extent of resection then can be determined. If necessary, the abdominal wall incision can be extended.

5. **Entrance into the Lesser Sac.** The posterior leaf of the omentum is attached to the transverse colon primarily by filmy adventitial tissue with some intervening small vessel tributaries. These attachments can be cut and coagulated electrosurgically to enter the lesser sac (Fig. 43-12.1). Dissection generally begins as far to the right as possible and continues as far to the left as possible. An open right-angle clamp guides the direction of the electrosurgical blade.

   Entrance into the lesser sac mobilizes the colon and provides access to the tumor-free proximal gastrocolic ligament. The omentum then is flipped over and held on distal traction.

FIGURE 43-12.1



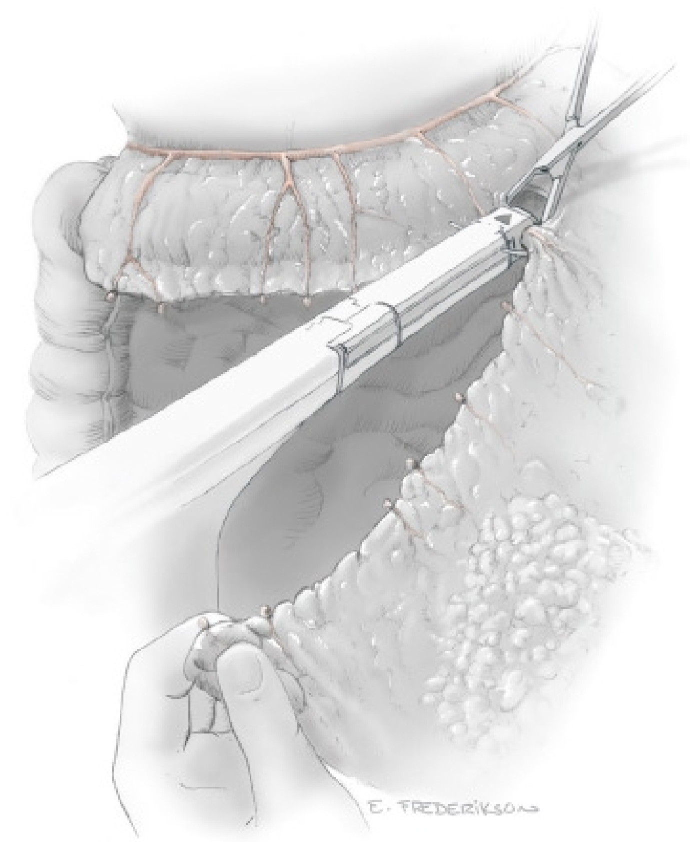
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Posterior dissection to enter the lesser sac.

6. **Gastrocolic Ligament Division.** Dissection again generally begins on the far right. Numerous vertically coursing vessels can be seen, but others are covered by fatty tissue and difficult to appreciate. A right-angle clamp is used by the surgeon to "pop" through an avascular portion of the gastrocolic ligament that is near to but safely distal from the colon. The clamp then is opened in a vertical direction (parallel to the vessels) and held in place to guide the LDS (linear dissecting stapler) (Fig. 43-12.2). This stapler incises tissues between its jaws and applies a row of fine vascular staples on both sides of the incision. The LDS is ideal because it is much faster than doubly clamping each pedicle of the gastrocolic ligament and placing individual suture ligatures.

   This procedure is continued across the entire gastrocolic ligament. Each pedicle of tissue is either divided with the LDS or is coagulated and cut electrosurgicallyâ€”depending on the apparent vascularity of the tissue. The omentum will need to be rotated back and forth intermittently to make certain that dissection remains away from the colon.

FIGURE 43-12.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Anterior ligation of gastrocolic ligament.

7. **Total Omentectomy.** In patients in whom an omental cake has extended proximally, supracolic (total) omentectomy is indicated. This procedure requires a midline vertical incision to provide better exposure to the upper abdomen. Resection simply may involve transecting the omentum at a higher level in the gastrocolic ligament. Alternatively, anatomic boundaries of resection may need to be extended to the hepatic flexure, the stomach, and the splenic flexure to encompass the entire tumor.

   Dissection again proceeds from right to left. Mobilization of the ascending colon around the hepatic flexure may be necessary. The right gastroepiploic artery is ligated with an LDS, and the dissection is continued to the left by dividing the short gastric vessels until the lateral-most portion of the tumor is reached. Mobilization of the descending colon and takedown of the splenic flexure may be required if tumor extends that far laterally. The omentum then is removed from the transverse colon by LDS ligature across the remaining gastrocolic ligament.

8. **Incision Closure.** The omentum should be re-examined at completion of surgery before closing the abdomen. Occasionally, small bleeding vessels or a hematoma will need to be addressed with additional ligation. The abdominal entry incision then is closed as described in Sections 41-1, Midline Vertical Incision or 41-2, Pfannenstiel Incision.

Postoperative

Nasogastric tube placement is required only if a total omentectomy has been performed. Decompression of the stomach for 48

hours protects the ligated gastric vessels from postoperative dislodgement from to gastric dilation. The remaining postoperative course follows that for laparotomy or for other specific concurrent surgeries performed.

43-13 SPLENECTOMY

In gynecologic oncology, removal of the spleen is required occasionally to achieve optimal surgical cytoreduction of metastastic ovarian cancer (Magtibay, 2006). Most commonly, tumor is found extending directly from the omentum into the splenic hilum during primary debulking surgery. Although splenectomy and other extensive upper abdominal resection techniques have been shown to improve survival, only 1 percent of patients actually will have their spleen removed during the initial operation (Eisenhauer, 2006; Goff, 2006). Splenectomy also is indicated for selected patients with isolated parenchymal recurrences to assist optimal secondary surgical cytoreduction of ovarian cancer (Chen, 2000). Lastly, intraoperative splenic trauma is the least common indication and is often unanticipated (Magtibay, 2006).

Preoperative

PATIENT EVALUATION

Preoperative diagnosis of splenic involvement is often difficult to predict prior to primary cytoreduction (Chen, 2000). Typically, in such cases, an omental cake is seen on computed tomographic (CT) scan, but its proximity to the spleen is difficult to ascertain. Splenic involvement is more commonly distinguishable at the time of secondary cytoreduction. Ideally, relapsed patients have isolated disease and an extended progression-free survival of at least 12 months before they are considered for splenectomy.

CONSENT

Patients with presumed advanced ovarian cancer should be consented for possible splenectomy, although the decision to perform the procedure will be finalized only intraoperatively. Removal of the spleen results in a longer operative time, greater blood loss, and longer hospital stay but ultimately may determine whether tumor is debulked optimally or not (Eisenkop, 2006). Possible complications include hemorrhage, infection, and pancreatitis.

Intraoperative

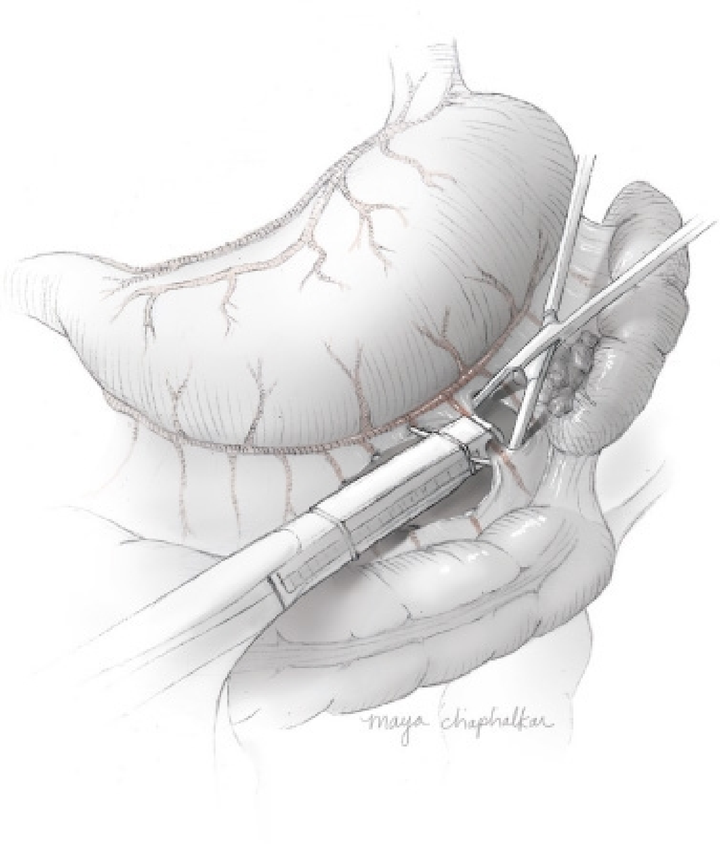
Surgical Steps

1. **Anesthesia and Patient Positioning.** Splenectomy is performed under general anesthesia and with the patient supine. As with other major intra-abdominal surgery, the abdomen is surgically prepared, and a Foley catheter is inserted.

2. **Abdominal Entry and Exploration.** Splenectomy generally requires a vertical incision for adequate exposure. Following entry, a surgeon should carefully assess the entire abdomen and pelvis to confirm the ability to resect all gross disease. Ideally, splenectomy is performed only if optimal tumor debulking can be achieved. The spleen is grasped to assess its mobility, degree of tumor involvement, and potential difficulty in removal.

3. **Entrance into the Lesser Sac.** The gastrocolic ligament is opened to the left of midline by dividing vascular pedicles with a ligate-divide-staple (LDS) device and transecting avascular filmy attachments with an electrosurgical blade. Dissection with the LDS stapler is continued in two directions: (1) superiorly to the transverse colon toward the splenocolic ligament and (2) inferiorly to the greater curvature of the stomach toward the gastrosplenic ligament (Fig. 43-13.1). The intervening portion of omentum often is involved with tumor.

FIGURE 43-13.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

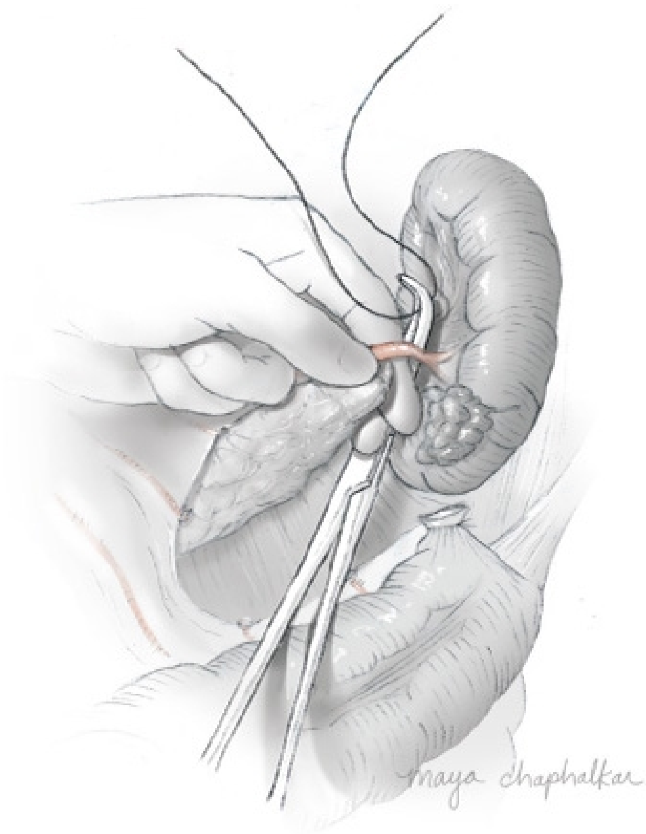
Mobilizing the spleen.

4. **Mobilization of the Spleen.** The spleen is grasped, elevated, and pulled medially to expose the splenophrenic ligament. The surgeon uses alternating electrosurgical blade and blunt finger dissection to mobilize the spleen. Additional blunt and sharp dissection then is performed circumferentially to free the spleen from the gastrosplenic and splenocolic ligaments.

5. **Ligating the Splenic Vessels.** The spleen is elevated into the incision, and the peritoneum overlying the splenic hilum then is incised carefully. To facilitate this approach, a left index finger is held against the spleen, and a thumb holds the pancreatic tail out of the dissecting plane. The pancreatic tail lies close to the splenic hilumâ€”often within 1 cm.

   Blunt dissection parallel to the expected course of the splenic artery and vein aids identification of these vessels. The artery, vein, and vascular tributaries should be ligated individually. The artery is isolated first to prevent splenic engorgement (Fig. 43-13.2). A right-angle clamp is placed beneath the artery, and a 2-0 silk suture is pulled through and tied. A second silk tie is placed more distally, directly at the hilum. The proximal end of the artery again is tied or occluded with a vascular clip. The artery then is divided, and the procedure is repeated for the splenic vein. Vascular tributaries should be divided similarly. The remaining peritoneal attachments are incised with an electrosurgical blade to remove the spleen.

FIGURE 43-13.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Vessel ligation.

6. **Final Steps.** The distal pancreas should be inspected carefully to exclude injury. The splenic vessels also should be re-examined prior to abdominal closure. Suspicion of trauma or bleeding should prompt placement of a suction drain in the splenic bed. Otherwise, drainage is not required routinely. A nasogastric tube is placed to decompress the stomach and prevent displacement of gastric vessel staples.

Postoperative

Hemorrhage is the most serious immediate complication and typically originates from the short gastric or splenic vessels. Bleeding from either site can be profuse and potentially catastrophic. Thus, the initial 12 to 24 postoperative hours require vigilance (Magtibay, 2006).

The most common postoperative complication is left lower lobe lung atelectasis. This typically will resolve with ambulation, pulmonary therapy, and time. Development of a postoperative intra-abdominal abscess usually results from inadvertent injury to the stomach, splenic flexure, or distal pancreas. Excessive pancreatic manipulation or laceration may lead to pancreatitis or leaking. If a drain has been placed, fluid may be sent to the laboratory if any of these complications are suspected.

Patients undergoing splenectomy will be at lifelong risk for episodes of overwhelming sepsis. Accordingly, the pneumococcal vaccinate should be administered routinely postoperatively (see Table 1-1). In addition, patients should be instructed to seek

immediate medical attention for fevers that may progress rapidly to serious illness.

43-14 DIAPHRAGMATIC SURGERY

Patients with advanced ovarian cancer often will have tumor implants or confluent plaques involving the diaphragm. The right hemidiaphragm is affected most frequently. Implants typically are superficial, but invasive disease can extend through the peritoneum to the underlying muscle. Accordingly, gynecologic oncologists should be prepared to perform diaphragmatic ablation, stripping, (peritonectomy), or full-thickness resection. These surgical procedures increase the rate of optimal tumor debulking and correlate with improved survival (Aletti, 2006a).

Preoperative

PATIENT EVALUATION

Imaging studies may suggest diaphragmatic nodularity, but the extent is difficult to ascertain until exploration in the operating room.

CONSENT

Patients with presumed advanced ovarian cancer should be informed of the possible need for extensive upper abdominal surgery to achieve optimal cytoreduction. Pulmonary complications are most common after diaphragmatic surgical techniques and include atelectasis, empyema, subphrenic abscess, pleural effusions, and pneumothorax (Cliby, 2004).

Intraoperative

INSTRUMENTS

It is generally advisable to have a cavitational ultrasonic surgical aspiration (CUSA) system and/or argon beam coagulator (ABC) available for ovarian cancer debulking procedures because one or both may be useful in eradicating diaphragmatic disease. These tools are discussed further in Chapter 40, Electrosurgery.

Surgical Steps

1. **Anesthesia and Patient Positioning.** As with other major intra-abdominal surgeries, diaphragmatic surgery requires general anesthesia. The patient is positioned supine, the abdomen is surgically prepared to accommodate an incision to the sternum, and a Foley catheter is inserted.

2. **Abdominal Entry.** Diaphragmatic surgery requires a vertical midline incision that has been extended to the sternum, passing to the right side of xyphoid, for maximum exposure. Following abdominal entry, the surgeon should assess the entire abdomen and pelvis carefully to confirm the ability to resect all gross disease. Ideally, diaphragmatic surgery is performed only if optimal tumor debulking can be achieved.

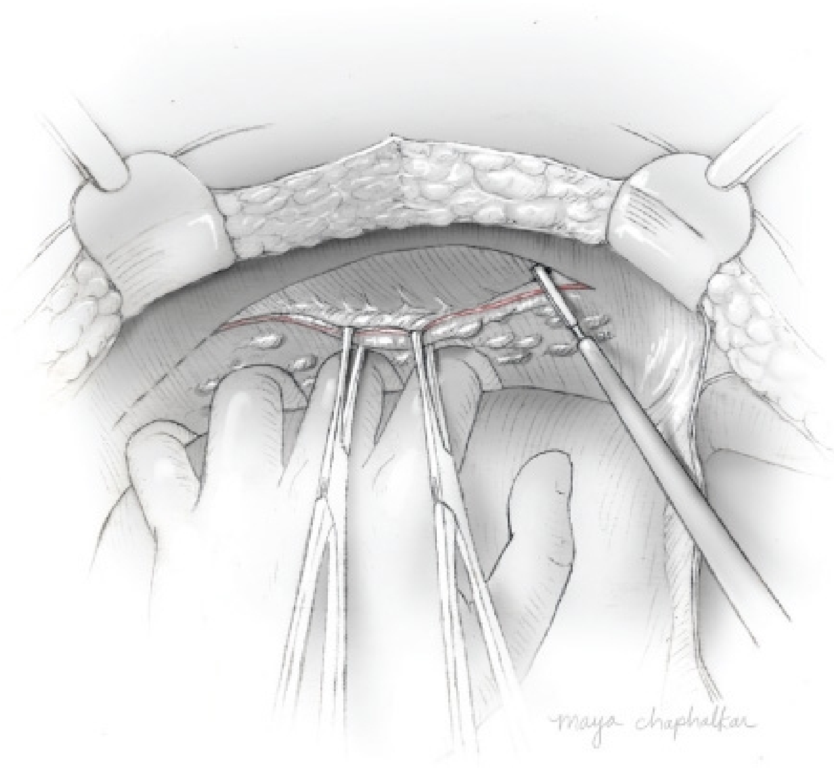
3. **Diaphragmatic Ablation.** A few scattered, small tumor implants on the surface of the right or left hemidiaphragm usually can be ablated easily with the CUSA or ABC. This simple technique may be all that is required.

4. **Diaphragmatic Stripping.** Confluent plaques of tumor or extensive implants indicate the need for resection of the peritoneum. The right side of the anterior rib cage is retracted sharply upward. The liver is retracted manually downward and medially to aid division of the falciform ligament with an electrosurgical blade, ligate-divide-staple (LDS) device, and/or clamps and delayed-absorbable suture ligation. This maneuver significantly mobilizes the liver and allows it to be held medially away from the diaphragm.

   Allis clamps are used to grasp the peritoneum above the tumor plaque and place it on tension. The peritoneal incision is created transversely with an electrosurgical blade, and a plane is developed with blunt dissection to separate the peritoneum from the underlying muscle fibers of the diaphragm. The free peritoneal edge is placed on tension with Allis clamps to maintain traction. The incision then is extended medially and laterally to encompass the implants (Fig. 43-14.1). The specimen eventually becomes large enough to grasp with a left hand to aid stripping of the peritoneum off the diaphragm. Electrosurgical blade dissection proceeds dorsally until all implants are contained within the peritoneal specimen. At this

point, it can be detached.

FIGURE 43-14.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Diaphragm stripping.

5. **Diaphragmatic Resection.** Occasionally, tumor has penetrated through the peritoneum, and a plane cannot be developed to strip the diaphragm. In these circumstances, full-thickness resection is required. A self-retaining retractor is placed, and the liver is mobilized. A transverse peritoneal incision is made above the tumor plaque, and at this point, the inadequacy of stripping is determined.

   The ventilator is turned off temporarily to avoid lung parenchymal injury, and an electrosurgical blade is used to cut through the diaphragmatic muscle into the pleural cavity above the tumor. Ventilation then may be resumed while Allis clamps are placed to retract the specimen into the peritoneal cavity. Both pleural and peritoneal surfaces should be visible to aid complete resection of the disease. Primary mass closure of the diaphragmatic defect then is performed with a running stitch using delayed-absorbable suture or interrupted stitches of silk suture.

   To evacuate the pneumothorax, a red rubber catheter is placed through the defect into the pleural space prior to securing the final knot. The ventilator is turned off at the end of inspiration to maximally inflate the lungs while the catheter is placed on suction. The catheter is removed concomitantly with tying the knot, and mechanical ventilation is resumed. Grafts typically are not needed, even for large defects (Silver, 2004).

6. **Final Steps.** The patient should be placed in the Trendelenburg position at completion of stripping or resection to check the

integrity of the diaphragmatic closure. The upper abdomen is filled with saline and observed for air leaks as the patient is ventilated. The presence of air bubbles indicates the need to reintroduce the red rubber catheter through the hole, resuture the defect, and retest the closure. Chest tubes are not required routinely.

Postoperative

Atelectasis is common with any diaphragmatic surgery. In addition, patients having full-thickness diaphragmatic resection are more likely to require postoperative ventilation and should be monitored carefully with chest radiographs for evidence of a pneumo- or hemothorax. These are generally manageable with chest tube drainage, lung re-expansion, and other supportive care measures.

43-15 COLOSTOMY

A colostomy creates a surgical anastomosis between created openings in the colon and anterior abdominal wall to divert bowel contents into an external collection bag. Colostomies serve several purposes and may be used to: (1) protect distal bowel repair from disruption or contamination by feces, (2) decompress an obstructed colon, and (3) evacuate feces if the distal colon or rectum is excised. In gynecologic oncology, there are innumerable specific indications for performing a colostomy. Some of the more common reasons include rectovaginal fistula, severe radiation proctosigmoiditis, bowel perforation, and rectosigmoid resection in which anastomosis is not feasible.

A colostomy may be temporary or permanent, and its duration is dictated by clinical circumstances. For instance, recurrent end-stage cervical cancer with obstruction may warrant a permanent colostomy. In contrast, only temporary diversion is needed to allow healing of an intraoperative bowel injury that occurred during benign gynecologic surgery.

In addition, the location of the stoma and the decision to perform an end or loop colostomy are also clinically based. A loop colostomy is constructed by creating an opening in a loop of colon and bringing both ends through the stoma. Alternatively, an end-colostomy stoma contains only the proximal end of the transected colon. The distal end is stapled and left intra-abdominally.

Regardless of the circumstances, the same surgical principles apply during colostomy: adequate bowel mobilization, sufficient blood supply, and a tension-free tunnel through the abdominal wall without bowel constriction. Strict attention to these seemingly straightforward steps will ensure the best possible outcome.

Preoperative

PATIENT EVALUATION

The colostomy site ideally is marked preoperatively by an enterostomal therapist to ensure that the postoperative stoma will be located in an easily accessible area when sitting and standing.

CONSENT

Concerns regarding postoperative quality-of-life changes are common with this procedure, and a surgeon should carefully describe a colostomy's medical purpose and its expected temporary or permanent duration. Many times, postoperative results are preferable to a patient's current symptoms and quality of life.

Perioperative complications may include fecal leakage into the abdomen or retraction of the stoma. Long-term complications involve parastomal hernia, stricture, and the potential need for surgical revision.

PATIENT PREPARATION

To minimize fecal contamination during bowel incision, aggressive bowel preparation such as with a polyethylene glycol with electrolyte solution (GoLYTELY). This is performed the day prior to surgery unless contraindicated, such as with bowel obstruction or perforation. Additionally, broad-spectrum antibiotics are given perioperatively because of possibility of stool contamination.

Intraoperative

Surgical Steps

1. **Anesthesia and Patient Positioning.** Colostomy is performed under general anesthesia with the patient positioned supine. Prior to surgery, the abdomen is surgically prepared, and a Foley catheter is inserted.

2. **Abdominal Entry and Exploration.** Colostomy generally requires a midline vertical incision for adequate exposure. The colon is elevated to ensure that it will reach the selected stoma site without tension. Dissection and adhesiolysis are performed as necessary to mobilize the bowel to obtain sufficient length before creating the abdominal wall stoma opening. If bowel fails to reach the selected site without tension despite adhesiolysis, then the stoma site is moved to accommodate bowel length.

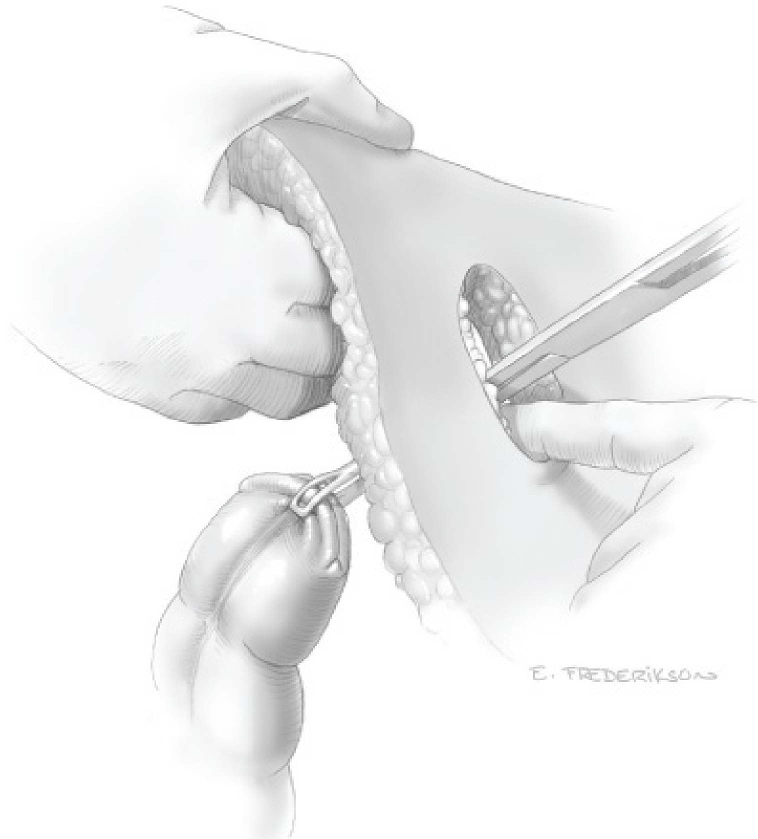
3. **End Colostomy.** This type of diversion is used commonly for rectovaginal fistulas and severe proctosigmoiditis after radiation. Ideally, a more distal colon site is used because bowel content becomes progressively more solid and less voluminous as it moves from the cecum to the rectum. Moreover, if performing an end sigmoid colostomy, the distal bowel simply may be stapled closed and left in the pelvis (Hartmann pouch). In contrast, a more proximal end colostomy will require that the distal bowel also be brought to the abdominal wall and opened to serve as a "mucus fistula" to prevent a closed-loop obstruction and subsequent colonic perforation.

   The stoma site for a sigmoid colostomy is selected based on an imaginary line drawn from the umbilicus to the left-sided anterosuperior iliac spine. The stoma is typically place at an approximate midpoint along this line. A Kocher clamp is used to elevate the skin, and an electrosurgical blade, set to a cutting mode, is used to remove a 3-cm circle of skin. The fascia is exposed by blunt dissection. In obese patients, a cone of subcutaneous fat may need to be removed to prevent bowel constriction. A cruciate incision is made on the anterior sheath. The fibers of the rectus abdominis muscle are separated bluntly, and another cruciate incision is cut on the posterior sheath. The opening is expanded bluntly to accommodate two to three fingers.

   After the colon is divided, the proximal bowel should be mobilized by incising the peritoneum toward the splenic flexure along the white line of Toldt. A Babcock clamp then is placed through the skin opening to grasp the stapled end of the bowel and lift it through the abdominal opening (Fig. 43-15.1). The bowel should appear pink, and its mesentery must not be twisted. The primary vertical abdominal incision then is closed.

   The stoma is "matured" by first tilting the table to the left to avert bowel spillage. The staple line is then excised. Circumferential interrupted 3-0 and 4-0 delayed-absorbable sutures are placed through the bowel mucosa and skin dermis (Fig. 43-15.2). The ostomy bag appliance then may be attached.

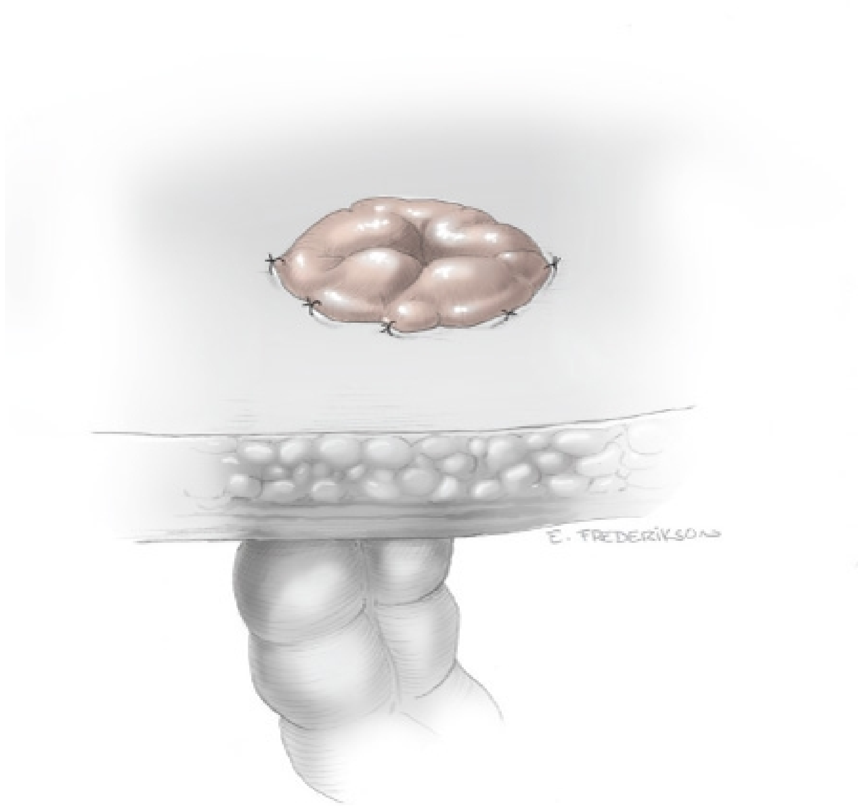
FIGURE 43-15.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

End-sigmoid colostomy: bowel pulled through abdominal wall incision.

FIGURE 43-15.2



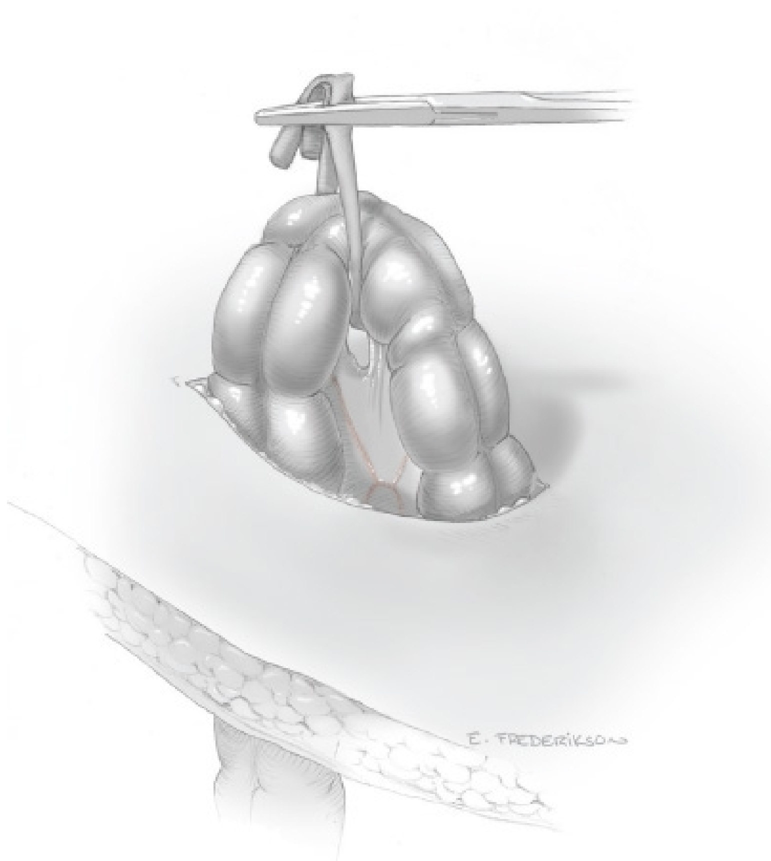
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

End-sigmoid colostomy: bowel mucosa sutured to skin.

4. **Loop Colostomy.** The usual indications for this type of procedure include protection of a distal anastomosis, relief of colonic obstruction, and treatment of colonic perforation. Accordingly, loop colostomy can be performed at any site along the colon where indicated. A loop colostomy in general is intended to be a temporary or palliative procedure. It is easier to take down, often simpler to perform, and does not necessarily require designation of loops as distal or proximal. However, fecal matter eventually will pass through to the distal segment, and as a result, this type of colostomy is not a permanent solution to a fistula or proctosigmoiditis.

   A transverse loop colostomy is performed in the left upper quadrant by making a 5-cm transverse incision over the rectus abdominis muscle midway between the costal margin and the umbilicus. The anterior and posterior fasciae, rectus abdominis muscle, and peritoneum are opened longitudinally by sharp and blunt dissection. The omentum is separated from the underlying transverse colon, and a 1/4 -in Penrose drain is placed through the mesocolon for traction. The bowel loop then is brought through the incision (Fig. 43-15.3). A Hollister bridge or similar device is passed through the mesenterotomy in place of the Penrose drain, and the incision is closed around the bowel loop without constricting it. The bowel is then "matured" by opening the antimesenteric half of the bowel along the tenia with an electrosurgical blade and leaving a 1-cm margin on each end (Fig. 43-15.4). The colostomy edges are sutured to the skin with interrupted stitches of 3-0 delayed-absorbable suture.

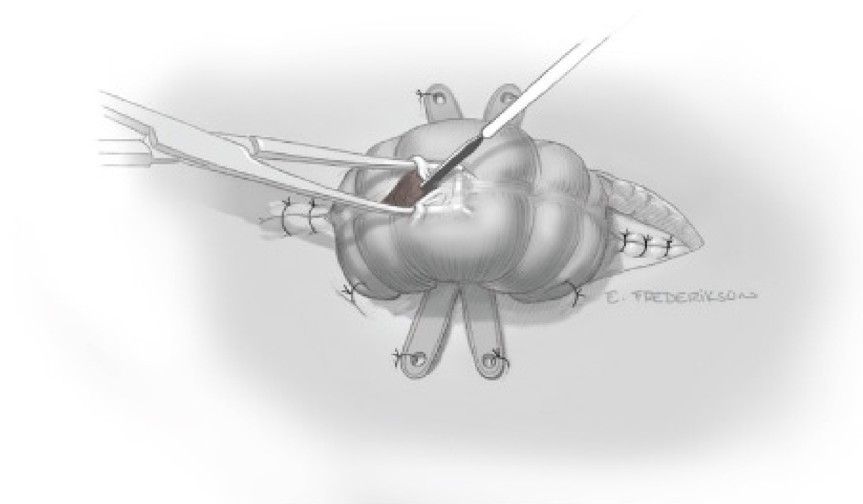
FIGURE 43-15.3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Transverse loop colostomy: elevation of bowel segment.

FIGURE 43-15.4



Transverse loop colostomy: opening of the bowel.

5. **Final Steps.** The stoma should be inspected carefully, and ideally, a stoma is pink and comfortably positioned. A dusky color may indicate bowel ischemia, which can lead to sloughing, necrosis, and retraction. Tension on the bowel may be improved with additional mobilization. Constriction of a loop colostomy within the abdominal wall opening can be improved by broadening the fascial incision or removing additional subcutaneous fat. On occasion, the tip of an end colostomy may need to be transected further distally to reach a viable bowel segment. All these steps are cumbersome but much easier to perform during the operation than postoperatively after complications have become obvious.

Postoperative

Morbidity is comparable for end and loop colostomies (Segreti, 1996b). Complications may be immediate or not evident for several months. Common complications specific to a colostomy may include wound infection, necrosis, bowel obstruction, hematoma, retraction, fistula, fecal leakage, sepsis, stricture, and parastomal herniation (Hoffman, 1992). Many of these complications are manageable with supportive care and local measures. Dramatic symptoms are infrequent but may require operative revision. Careful attention during initial surgery will prevent most of these morbidities.

43-16 LARGE BOWEL RESECTION

Partial colectomy is performed most often as part of cytoreductive surgery for ovarian cancer. Other indications include radiation injury and colonic fistulas. Surgical principles are similar, whether a bowel segment to be removed is from the ascending, transverse, or descending colon. Rectosigmoid (low anterior) resection is somewhat more complex and is reviewed in Section 43-19, Low Anterior Resection.

Ideally, during colectomy, a surgeon will achieve meticulous hemostasis, remove the smallest required length of colon, avoid fecal spill, and exclude proximal or distal intestinal obstruction. In addition, bowel must be sufficiently mobilized to create a tension-free anastomosis that is watertight, large caliber, and supported by adequate blood supply.

A general familiarity with colonic blood supply is important for partial colectomy. The ascending and transverse colons are supplied by the superior mesenteric artery via the middle colic, right colic, and ileocolic branches. The descending and sigmoid colons are supplied by the left colic and sigmoid branches of the inferior mesenteric artery. As a result, these vessels form an effective anastomotic vascular network that allows large bowel resection at virtually any segment of the colon.

Preoperative

PATIENT EVALUATION

The need for partial colectomy during ovarian cancer cytoreductive surgery usually is decided intraoperatively and is based on clinical circumstances. For example, although a preoperative computed tomographic (CT) scan may suggest tumor at multiple sites near the colon, these lesions often are superficial and may be removed without colectomy. Typically, the need for colectomy is more obvious preoperatively for those with radiation damage or fistulas, but the extent of the resection still generally will be unclear until the operation is underway.

CONSENT

Patients should be fully informed of the potential for colostomy, for anastomotic leak, and for abscess formation. A postoperative ileus also should be anticipated.

PATIENT PREPARATION

To minimize fecal contamination during bowel incision, aggressive bowel preparation such as with a polyethylene glycol with electrolyte solution (GoLYTELY) is performed the day prior to surgery unless contraindicated, such as with bowel obstruction or perforation. However, if a bowel obstruction is present, then cleansing the distal colon with enemas is a secondary option. The patient also should be marked for a colostomy if this is possibility. Moreover, if a complicated resection or prolonged recovery is anticipated, total parental nutrition (TPN) administration should be considered. Antibiotic prophylaxis may be initiated prior to creating the abdominal incision.

Intraoperative

INSTRUMENTS

To prepare for complicated resections, a surgeon should have access to all types and sizes of bowel staplers, which include end-to-end anastomosis (EEA), gastrointestinal anastomosis (GIA), and transverse anastomosis (TA) staplers. Additionally, a ligate-divide-staple (LDS) device may be used for vessel ligation.

Surgical Steps

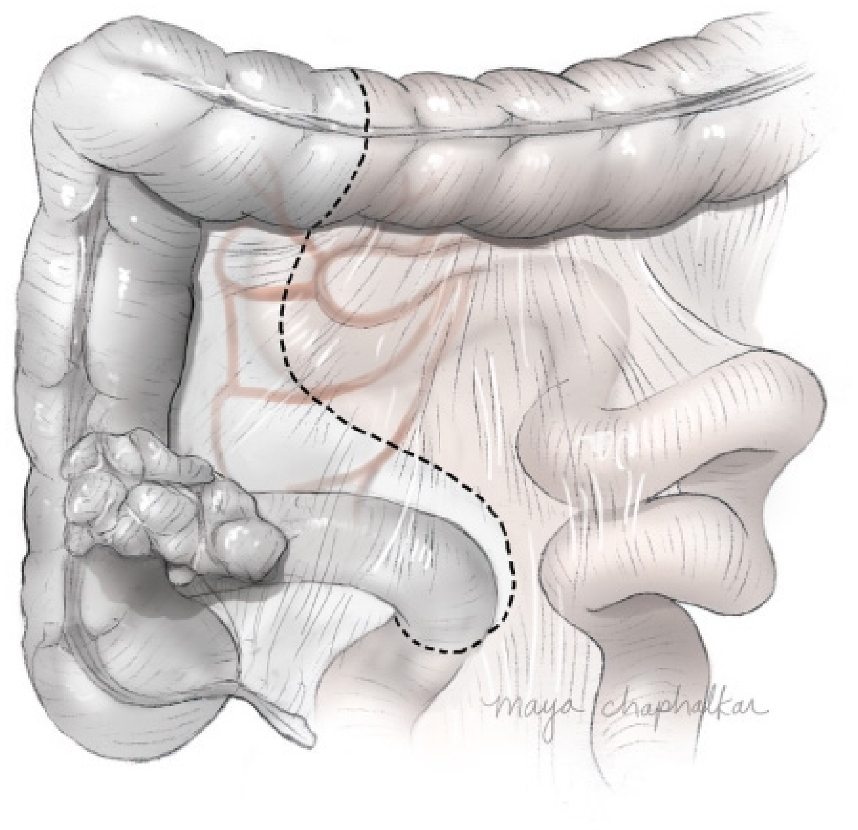
1. **Anesthesia and Patient Positioning.** Rectovaginal examination under anesthesia is mandatory before positioning any patient for abdominal gynecologic cancer surgery. A palpable mass with compression of the rectum or rectovaginal septum indicates the need for dorsal lithotomy with legs comfortably positioned in Allen stirrups to prepare for possible low anterior resection and anastomosis (see Section 43-19, Low Anterior Resection). Supine positioning is otherwise appropriate. Sterile preparation of the abdomen, perineum, and vagina is completed, and a Foley catheter is placed.

2. **Abdominal Entry.** A midline vertical incision is preferable if partial colectomy is anticipated to provide access to the entire abdomen. Required dissection, adhesiolysis, or other unanticipated findings may render transverse incision exposure inadequate.

3. **Exploration.** The surgeon should explore the entire abdomen first to lyse adhesions, to "run" the bowel and evaluate its appearance from duodenum to rectum, to exclude other potential sites of obstruction, and to determine the extent of the bowel resection. Blood supply at the splenic flexure, hepatic flexure, and ileocecal valve can be tenuous. As a result, resection boundaries should lie beyond these areas if possible. For example, in Fig. 43-16.1, because of the limited blood supply at the hepatic flexure, the proximal line of transection includes several centimeters of transverse colon. Similarly, the distal line of transection includes 8 to 10 cm of the terminal ileum because the ileocecal artery is sacrificed.

   A window is made in the mesocolon proximal and distal to the lesion. A 1/4 -in Penrose drain is pulled through each locations' opening to provide traction.

FIGURE 43-16.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Area of resection is shown to encompass the tumor.

4. **Mobilization of the Colon.** The bowel is next mobilized. This is performed by incising peritoneum along the white line of Toldt and/or the hepatic or splenic flexuresâ€"depending on the resection site. The left or right retroperitoneal space is entered beyond the distal Penrose drain by creating an opening with an electrosurgical blade just lateral to the colon. This space is expanded bluntly, and electrosurgical dissection is guided cephalad past the proximal Penrose drain while providing countertraction on the colon. The bowel segment may be mobilized bluntly medially as necessary. Omentectomy may be required for resections involving the transverse colon (see Section 43-12, Omentectomy).

5. **Resection.** A GIA stapler is inserted to replace one Penrose drain, is positioned around the entire colon diameter, and is fired. A second stapling and transection then are repeated at the other site. The bowel segment then may be detached from the underlying mesentery using an LDS device or individual clamps and delayed-absorbable suture ligation. During this process, as much of the mesentery as possible should be preserved. The specimen then is removed.

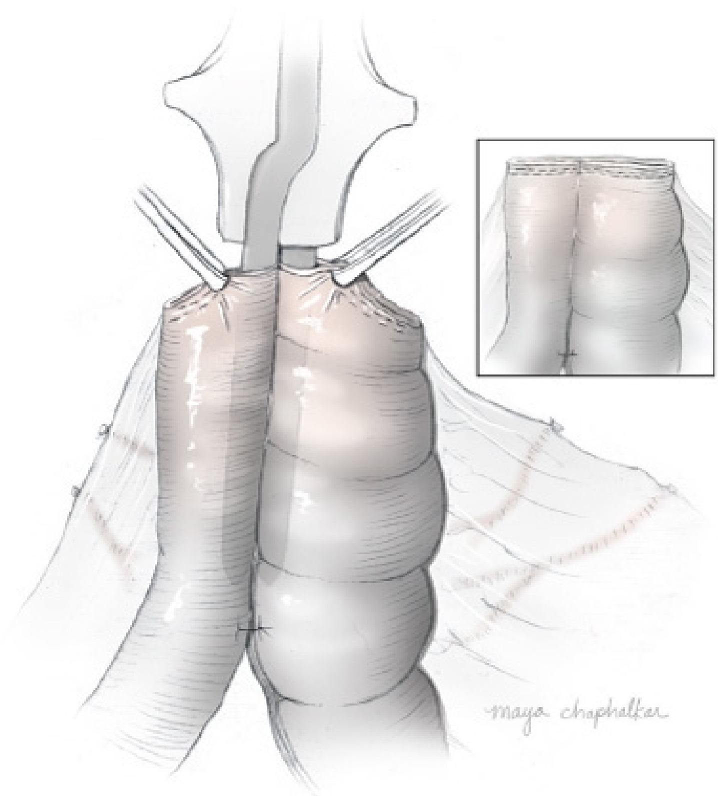
6. **Side-to-Side Anastomosis.** The remaining proximal and distal bowel ends are held against each other to estimate their position following anastomosis. Typically, additional mobilization of the bowel by incising adhesions and peritoneum is required using a combination of electrosurgical blade and blunt dissection. The two segments must comfortably approximate antimesenteric borders without tension. The proximal and distal stapled bowel ends are cleared of fatty tissue to create an anastomosis with maximal mucosa-to-mucosa contact. To accomplish this, the proximal staple line is elevated with two Allis clamps at its lateral edges. Debakey forceps place surrounding fatty tissue on traction, and an electrosurgical blade is used to

dissect this away from the bowel serosa. The dissection then is performed on the distal segment in similar fashion.

The staple lines are excised with scissors, and the bowel is held vertically to prevent fecal spill. One fork of the GIA stapler then is inserted as deeply as possible into one of the bowel lumens (Fig. 43-16.2). The bowel segments are evenly positioning, and the device is fired along the antimesenteric surfaces and removed. This stapler places two staggered rows of titanium staples and simultaneously transects tissue between these rows.

The bowel interior should be examined for bleeding sites, which may be coagulated electrosurgically. The remaining opening then may be stapled across with a TA stapler (see Fig. 43-18.3). Residual bowel tissue above the TA staple line is excised. The mesenteric defect is re-approximated with interrupted or running delayed-absorbable suture to prevent an internal hernia.

FIGURE 43-16.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

GIA stapler connects a side-to-side anastomosis of the antimesenteric surfaces of the ileum and transverse colon. **Inset:** TA stapler line closes the distal end of the anastomosis.

7. **Final Steps.** The abdomen is irrigated with copious warmed saline at the conclusion of any bowel resection, especially if feces have spilled during the procedure. Drains are not required routinely and may impair healing.

Postoperative

Morbidity after large bowel resection is increased significantly by a variety of factors but especially by pre-existing obstruction,

malignancy, and sepsis. Anastomotic leaks are the most specific complication and typically present as an abscess, a fistula, or as peritonitis within days or weeks of surgery. Some localized leaks can be managed with initiation of total parenteral nutrition (TPN), CT-guided drainage, antibiotic administration, and bowel rest. However, urgent reoperation is indicated for nonlocalized intraperitoneal perforation and its resulting peritonitis. This usually will require colostomy (Hoskins, 1987).

Pelvic abscesses also may result from intraoperative fecal spillage or hematoma superinfection. Usually these will resolve with CT-guided drainage and antibiotics. Gastrointestinal hemorrhage should be rare with stapled procedures. In addition, symptomatic anastomotic strictures are infrequent and often present as colonic obstruction. Some strictures can be managed with endoscopic stents, but often they require re-operation. Small or large bowel obstructions also may result from postoperative adhesions or tumor progression. Lastly, a prolonged ileus can develop and be very slow to resolve. Most of these complications will depend primarily on the patient's underlying nutrition and the clinical circumstances prompting the primary surgery.

43-17 ILEOSTOMY

Relatively few patients will require ileostomy for management of a gynecologic malignancy. For those who do, loop ileostomy usually is a temporary procedure that is performed to protect a distal anastomosis (Nunoo-Mensah, 2004). In addition, diversion of a colonic fistula or palliation of a large bowel obstruction may be other indications (Tsai, 2006). On occasion, ovarian cancer will involve the entire colon, requiring colectomy with a permanent end ileostomy and formation of a Hartmann pouch (Weber, 1994).

Preoperative

PATIENT EVALUATION

Stoma placement is particularly important for an ileostomy because the effluent will be more corrosive than that of a colostomy. The stoma site is selected based on an imaginary line drawn from the umbilicus to the left-sided anterosuperior iliac spine. The stoma is typically place at an approximate midpoint along this line. Ideally, the site should be marked by an enterostomal therapist preoperatively.

CONSENT

In general, many of the complications of this procedure mirror those of colostomy: retraction, stricture, obstruction, and herniation. Patients should be informed that temporary loop ileostomies can be taken down later without a laparotomy.

PATIENT PREPARATION

Bowel preparation is preferred whenever there is a potential for bowel resection. However, ileostomy can be performed without an increased risk of infection without preoperative bowel cleansing.

Intraoperative

Surgical Steps

1. **Anesthesia and Patient Positioning.** Ileostomy is performed under general anesthesia. Patients generally are supine, but dorsal lithotomy or other positioning with access to the abdominal wall is acceptable.

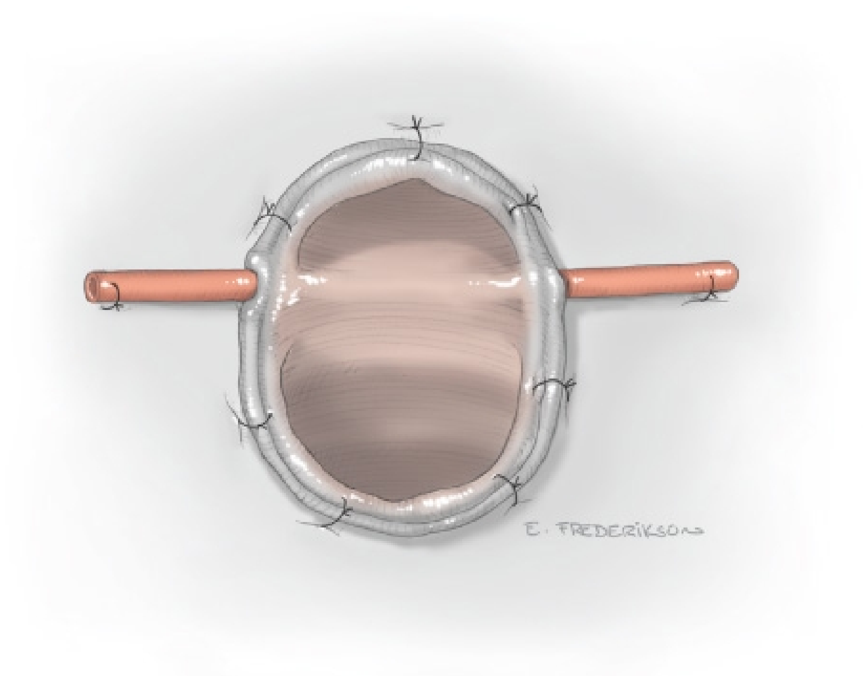
2. **Abdominal Entry.** A midline vertical incision is preferable for most situations in which an ileostomy is considered.

3. **Exploration.** After abdominal entry, the surgeon should first explore the abdomen, lyse adhesions, "run" the bowel length to identify obstructive sites, and determine the need for ileostomy. An ileum loop is selected that will reach several centimeters above the skin. Additionally, to reduce the effluent volume, the selected loop should be located as distally along the bowel length as possible. On occasion, tethering of small bowel by carcinomatosis or radiation injury will significantly reduce mobility and require a more proximal diversion.

4. **Loop Ileostomy.** A 1/4 -in Penrose drain is placed through a mesenterotomy at the selected loop's apex. The loop then can be approximated to the stoma site, which is created to accommodate two fingers, as described for an ileal conduit (see Section 43-6, Incontinent Urinary Conduit, Step 6). The loop is pulled through the abdominal wall opening so that several

centimeters protrude above the skin surface. The Penrose drain is removed and replaced with either the cut end of a red rubber catheter or other device that can be sewn to the skin to elevate the loop (Fig. 43-17.1). The loop should be tension-free and patent. Its proximal end is positioned lower to reduce fecal flow into the distal bowel. The abdominal wall then is closed around the stoma. The ileostomy is "matured" by longitudinally incising the bowel loop and everting its walls with Allis clamps. Circumferential interrupted stitches of 3-0 and 4-0 delayed-absorbable sutures are placed through the dermis and bowel mucosa. An ostomy bag then may be applied.

FIGURE 43-17.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Ileal loop has been pulled through the abdominal wall and opened with cautery.

Postoperative

The stoma should be examined carefully postoperatively for its appearance and function. The supporting rod may be removed in 1 to 2 weeks but potentially earlier if the stoma becomes dusky or the loops seem constricted or are obstructed.

Ileostomy may be associated with significant postoperative complications. High-output effluent also may result in electrolyte abnormalities that are difficult to correct. In addition, approximately 10 percent of patients will require early re-operation for small bowel obstruction or intra-abdominal abscess (Hallbook, 2002). Specifically, if loop ileostomy is indicated to protect a low anterior anastomosis, it is more commonly associated with bowel obstruction and ileus than loop colostomy (Law, 2002). Long-term complications such as a peristomal hernia and retraction are also possible.

43-18 SMALL BOWEL RESECTION

There are numerous indications for small bowel resection in gynecologic oncology, including obstruction, involvement with cancer, perforation, intraoperative injury, fistulas, and radiation damage. Unlike the large bowel, where greater attention is required to ensure an adequate blood supply to the anastomotic site, the small intestine has a consistent cascade of vessels that all arise from the superior mesenteric artery. However, unique situations such as radiation damage, obstructive dilatation, and edema can

compromise this vasculature dramatically. In these situations, meticulous dissection is especially crucial to prevent inadvertent removal of the bowel serosa, enterotomy, and bowel damage that will impair anastomotic healing. In general, surgical principles with this procedure are much the same as those for large bowel resection (see Section 43-16, Large Bowel Resection).

Preoperative

PATIENT EVALUATION

Small bowel obstructions (SBO) that do not resolve with nasogastric suction decompression and bowel rest may result from postoperative adhesions or tumor progression. Patients with recurrent gynecologic malignancy, particularly those with ovarian cancer, should be evaluated with an upper gastrointestinal series and small bowel follow-through radiographic studies preoperatively. With these, numerous sites of obstruction may be identified that would indicate a woman with end-stage disease who might be better served by placement of a palliative percutaneous draining gastrostomy tube. Patients with an SBO following pelvic radiation almost invariably have stenosis at the terminal ileum.

CONSENT

Depending on circumstances, patients should be counseled about the intraoperative decision-making process for performing an anastomosis, bypass, or ileostomy. Leaking and/or fistula formation are possible complications. Less common outcomes include re-obstruction, short bowel syndrome, and vitamin B_{12} deficiency.

PATIENT PREPARATION

Aggressive bowel preparation such as with a polyethylene glycol with electrolyte solution (GoLYTELY) performed the day prior to surgery is ideal but may be contraindicated in patients with obstruction. Antibiotic prophylaxis should be initiated. If a complex fistula is present or an extensive resection for radiation damage is anticipated, then total parental nutrition (TPN) may be advisable.

Intraoperative

The small intestine can be damaged easily by rough handling and extensive blunt dissectionâ€”particularly if it is edematous or previously radiated. Trauma should be kept to an absolute minimum to reduce spillage of intestinal contents and avoid postoperative sepsis.

INSTRUMENTS

The surgeon should have access to all types and sizes of bowel staplers, such as end-to-end anastomotic (EEA), gastrointestinal anastomotic (GIA), and transverse anastomotic (TA) staplers, to prepare for complicated resections.

Surgical Steps

1. **Anesthesia and Patient Positioning.** Small bowel resection is performed under general anesthesia. Patients are generally supine, but dorsal lithotomy or other positioning with access to the abdominal wall is acceptable.

2. **Abdominal Entry.** A midline vertical incision is preferable for most situations in which an small bowel resection is considered.

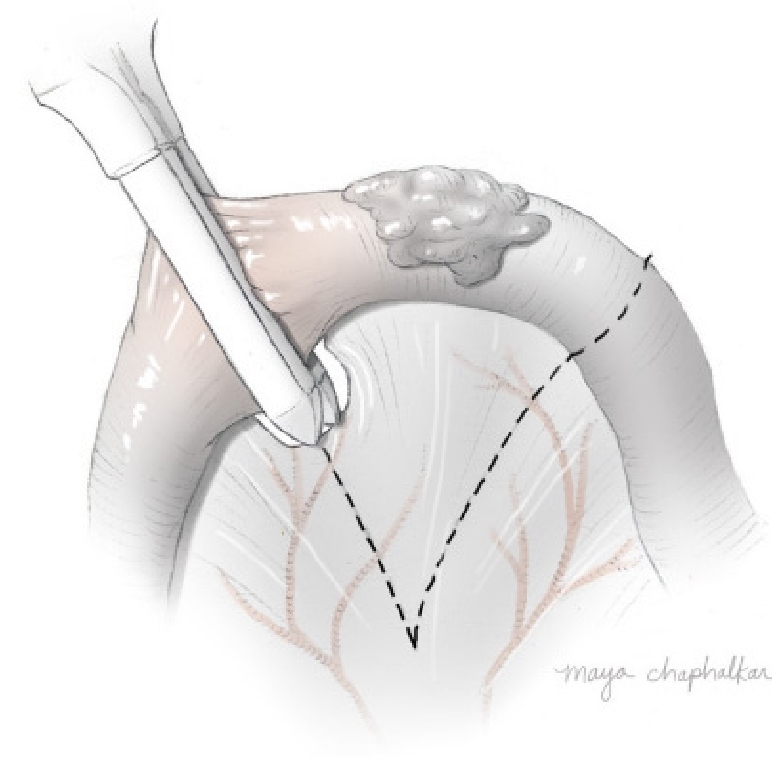
3. **Exploration.** The surgeon should explore the entire abdomen first to identify the obstruction. Infrequently, an adhesion may be located and lysed to relieve an obstruction and completely avoid small bowel resection. More often, an area is discovered that warrants removal. Additionally, the remainder of the bowel should be examined to exclude other obstructive sites.

   Peritoneum and adhesions attached to the involved portion of small bowel are transected to mobilize the bowel. Ideally, healthy-appearing serosa for anastomosis is identified both proximal and distal to the lesion while preserving a maximum amount of intestine.

4. **Dividing Small Bowel.** The bowel is brought through the incision. A 1/4 -inch Penrose drain is pulled through a mesenterotomy at the proximal and distal sites. A GIA stapler is inserted to replace the Penrose drain, fired, and repeated on the other site (Fig. 43-18.1). These staple lines minimize contamination of the abdomen with bowel contents.

A wedge of mesentery then is "scored" by superficially creating a V shape with an electrosurgical blade. The mesentery is divided by an LDS device and/or clamps and delayed-absorbable sutures ligatures. Hemostasis will be more difficult with edematous or inflamed tissue, and thus smaller pedicles should be divided. The bowel specimen is removed.

FIGURE 43-18.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

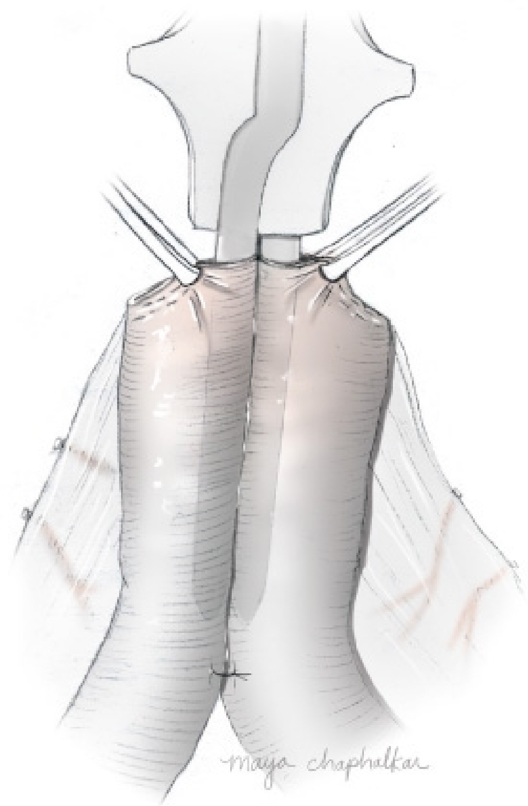
Identifying the proximal and distal sites.

5. **Performing Side-to-Side Anastomosis.** The proximal and distal bowel segments are elevated with Allis clamps and matched along their antimesenteric borders. A single silk stay suture is placed through the antimesenteric border of each segment beyond the tip of where the GIA stapler fork will reach. The antimesenteric corner of each segment is excised just deeply enough to enter the lumen and sufficiently wide to permit passage of one GIA stapler fork. Massively distended bowel from an obstruction may be decompressed by inserting a pool suction tip into the proximal end.

   Allis clamps are replaced on the bowel at the edge of the each opening. These clamps and silk stay sutures assist insertion of one fork of the GIA stapler into each segment and aid bowel positioning (Fig. 43-18.2). The bowel is rotated to bring the antimesenteric borders together, Allis clamps are removed, and the GIA stapler is closed and fired.

   The remaining enterotomy is regrasped with three Allis clamps to approximate closure. The TA stapler is placed around the bowel beneath the Allis clamps and is closed (Fig. 43-18.3). The Allis clamps elevate the enterotomy and assist correct positioning of the TA stapler. The stapler is fired, excess tissue is trimmed sharply, and the stapler is opened and removed. The mesenteric defect may be closed next with running delayed-absorbable suture to prevent internal herniation.

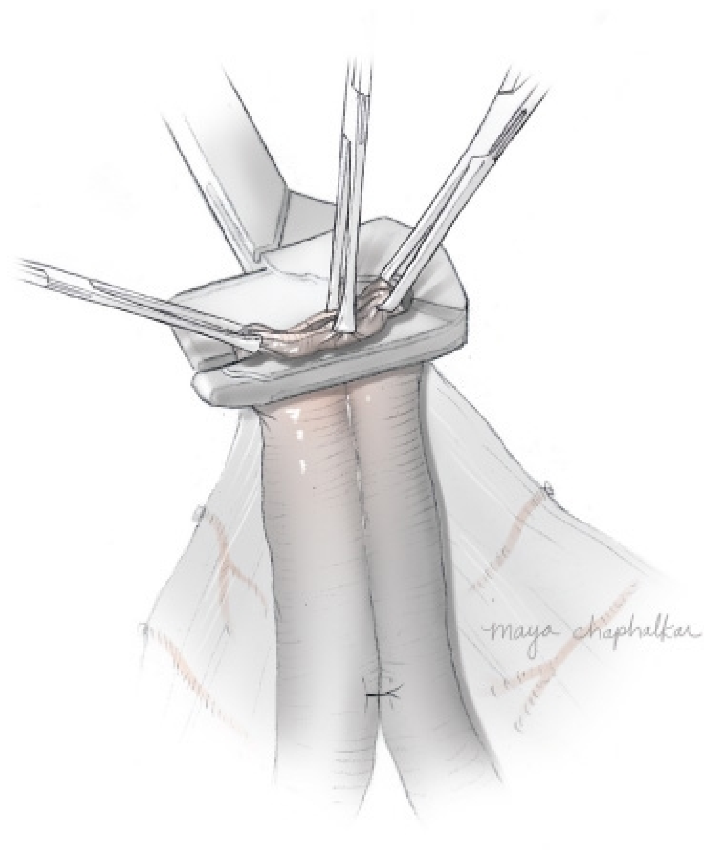
FIGURE 43-18.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Side-to-side anastomosis.

FIGURE 43-18.3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Closing the enterotomy.

6. **Final Steps.** Copious irrigation with warmed saline should be performed at the conclusion of any bowel resection, but particularly if spillage is noted during the procedure. Drains are not required routinely and may impair healing. In general, placement of a nasogastric tube to decompress the stomach postoperatively until bowel function has resumed is prudent.

Postoperative

The underlying health of the patient, diagnosis, and indications for small bowel resection will dictate much of the potential postoperative morbidity. Common minor complications include wound infection and ileus. Fistula formation, anastomotic leakage, and obstruction are more serious problems that may require re-operation. Two specific complications are unique to extensive small bowel surgery.

First, short bowel syndrome may follow resection. With resection, more than half of the small intestine can be removed without impairing nutritional absorption as long as the remaining bowel is functional. Accordingly, this syndrome is more likely is to develop from extensive radiation damage than resection. Symptoms include diarrhea and dehydration. Maldigestion, malabsorption, nutritional deficiencies, and electrolyte imbalance are noted commonly. As a result, home parenteral nutrition may be required in some patients (King, 1993).

A second complication, vitamin B_{12} deficiency results from inadequate absorption and depletion of available stores. Vitamin B_{12} and bile salts are only absorbed in the distal 100 cm of the ileum. Malabsorption in this segment may result from radiotherapy or intestinal resection (Bandy, 1984). In these patients, long-term intramuscular vitamin B_{12} injections are required.

43-19 LOW ANTERIOR RESECTION

Rectosigmoid resection, also known as *low anterior resection,* is used mainly in gynecologic oncology to achieve optimal cytoreduction of primary or recurrent ovarian cancer (Mourton, 2005). This procedure is distinguished from other types of large bowel resections in that it requires mobilization of the rectum and transection of the rectum distally, below the peritoneal reflection. Following resection of the involved rectosigmoid segment, proximal and distal bowel ends usually are then reanastomosed.

Low anterior resection is the most common bowel operation for primary debulking (Hoffman, 2005). For example, en bloc pelvic resection combines low anterior resection with hysterectomy, bilateral salpingo-oophorectomy, and removal of surrounding peritoneum (see Section 43-11, En Bloc Pelvic Resection) (Clayton, 2002). In addition, total and posterior pelvic exenterations incorporate the principles of low anterior resection to remove centrally recurrent cervical cancer with widely negative soft tissue margins (see Sections 43-3, Total Pelvic Exenteration and 43-5, Posterior Pelvic Exenteration). Other less common indications for low anterior resection are radiation proctosigmoiditis and intestinal endometriosis (Urbach, 1998). Occasionally, additional large or small bowel resections will be performed concomitantly with low anterior resection (see Sections 43-16, Large Bowel Resection and Section 43-18, Small Bowel Resection) (Guidozzi, 1994).

Preoperative

PATIENT EVALUATION

Bowel symptoms may or may not be present in women with rectosigmoid involvement of ovarian cancer. However, the surgeon should have high suspicion if patients describe rectal bleeding or progressive constipation. A rectovaginal examination may help to predict the need for low anterior resection. Additionally, CT scanning may suggest rectosigmoid invasion of tumor. However, prior to surgery, prediction is difficult. Many ovarian cancers intraoperatively may be easily lifted away from the bowel and surface tumors may be removed without resection.

CONSENT

Patients should be prepared for the possibility of low anterior resection any time ovarian cytoreductive surgery is discussed. The survival benefit of achieving minimal residual disease warrants the risks of this procedure. However, low anterior resection extends operative time significantly, and hemorrhage may contribute to a need for blood transfusion (Tebes, 2006).

In general, progressively higher complication rates and poorer long-term bowel function follow more distal anastomoses that approach the anal verge. However, the operation is designed to encompass the tumor, and an end-sigmoid colostomy with Hartmann pouch is another, albeit less attractive, option for very low resections.

In general, a protective loop colostomy or ileostomy is not required, but patients should be counseled for this possibility (see Sections 43-15, Colostomy and 43-17, Ileostomy). Anastomotic leaks should develop in fewer than 5 percent of patients (Mourton, 2005).

PATIENT PREPARATION

To minimize fecal contamination during resection, bowel preparation such as with a polyethylene glycol with electrolyte solution (GoLYTELY) is mandatory prior to surgery. Antibiotic prophylaxis may be initiated in the operating room.

Intraoperative

INSTRUMENTS

All types and sizes of bowel staplers such as end-to-end anastomosis (EEA), gastrointestinal anastomosis (GIA), and transverse anastomosis (TA) staplers should be available. Additionally, a ligate-divide-staple (LDS) device may be used for vessel ligation.

Surgical Steps

1. **Anesthesia and Patient Positioning.** Low anterior resection typically requires general anesthesia. Rectovaginal examination under anesthesia is mandatory before positioning any patient for abdominal gynecologic cancer surgery. A palpable mass with compression of the rectum or rectovaginal septum warrants patient positioning in the dorsal lithotomy

position with the legs comfortably placed in Allen stirrups. This allows access to the rectum in patients requiring EEA stapler insertion for anastomosis. Alternatively, supine positioning may be appropriate if no mass is palpable by rectovaginal examination. In such cases, if a mass is located more proximally, low rectal anastomosis can be performed entirely within the pelvis.

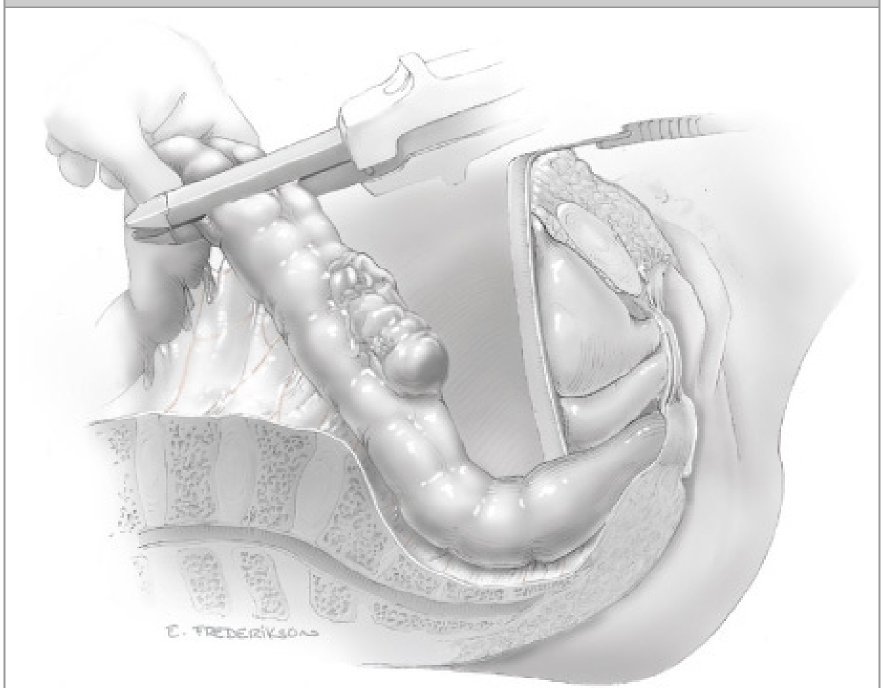
2. **Abdominal Entry.** A midline vertical incision provides generous operating space and upper abdominal access. This is preferable if low rectal anastomosis is anticipated because the descending colon may need to be mobilized around and beyond the splenic flexure. In contrast, transverse incisions often fail to provide sufficient exposure.

3. **Exploration.** The surgeon should explore the entire abdomen first to determine if disease is resectable. If not, then the procedure's benefit should be re-evaluated. On occasion, imminent bowel obstruction, infection, or other clinical circumstances may dictate resection regardless of residual tumor. The pelvis and rectosigmoid should be palpated to plan for the resection and determine whether en bloc pelvic resection or an exenterative procedure is indicated.

4. **Visualization.** The bowel is packed into the upper abdomen, and retractor blades are positioned to allow access to the deep pelvis and the entire rectosigmoid colon. Ureters are identified at the pelvic brim and held laterally on Penrose drains to expose the peritoneum and mesentery, which can be safely dissected next.

5. **Dividing the Proximal Sigmoid.** The sigmoid colon is held on traction proximal to the tumor and in the approximate area where it will be divided. The ureter is located, and a right-angle clamp is used to guide superficial electrosurgical blade dissection of the peritoneum and mesentery up to the bowel serosa. This is repeated on the other side. Blunt dissection then may be performed to define the entire circumference of the sigmoid. Epiploica and adjacent fatty tissue are held with Debakey forceps and dissected away with an electrosurgical blade from the proposed area of transection. The GIA stapler is placed across the sigmoid, fired, and removed (Fig. 43-19.1).

FIGURE 43-19.1



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Dividing the proximal end.

6. **Dividing the Mesentery.** The entire mesentery now may be divided to provide access to the avascular plane between the rectosigmoid and the sacrum (retrorectal space). Gentle blunt dissection is performed inferior to the divided sigmoid to better characterize the underlying fatty tissue and small vessels. A right-angle clamp is placed through sections of the mesentery, and an LDS device divides this tissue. Dissection is continued anteroposteriorly through approximately two-thirds of the mesentery. Typically, one or more pedicles will have a blood vessel that slips out and requires clamping with a right-angle clamp and ligation with delayed-absorbable suture.

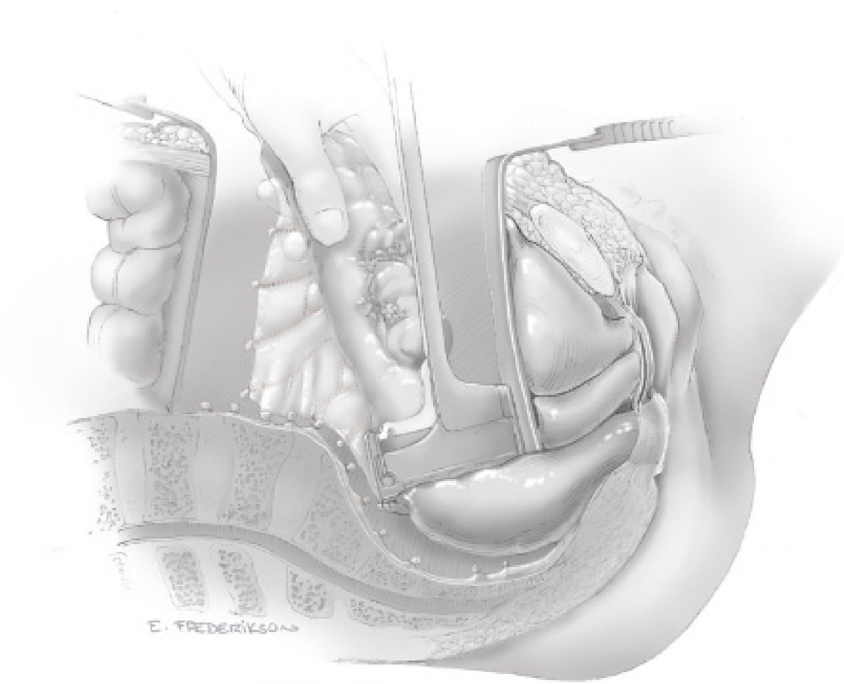
   Blunt dissection is performed in the pelvic midline to identify the large superior rectal vessels (branches of the inferior mesenteric artery [IMA]). This artery and vein are large and should be separately doubly clamped, cut, and ligated with delayed-absorbable suture. Dissection is continued to the other side of the pelvis until there is no tissue visible between the ureters. The common iliac artery bifurcation and sacrum should be entirely visible.

7. **Dividing the Rectum.** The proximal sigmoid and attached mesentery are repacked into the upper abdomen to improve pelvic exposure. The rectosigmoid is held superiorly, and blunt dissection is performed posteriorly in the retrorectal space to mobilize the distal bowel beyond the tumor to define the location of planned resection. The ureters are traced along the pelvic sidewall. Lateral blunt dissection is performed to further mobilize the rectosigmoid. Lateral mesenteric attachments are isolated and divided with an LDS device or grasped between Pean clamps, cut, and ligated. Self-retaining retractor blades may require repositioning as dissection proceeds more distally.

   The anterior bowel serosa generally is visible throughout its course beyond the peritoneal reflection and into the levator muscles. Lateral and posterior bowel margins are surrounded by fatty tissue, mesentery, and rectal pillars. The distal rectum beyond the tumor is grasped and rotated to aid exposure of these attachments. Alternating electrosurgical blade dissection, LDS division, and/or right-angle clamping and transection are used circumferentially until the rectal serosa is entirely visible.

   The rectosigmoid is held on traction, and the pelvis is re-examined to determine which size TA stapler is suitable and whether a roticulator will be required to fit into the space. A roticulator serves as a mobile joint for the stapler and, within a confined space, permits perpendicular positioning of the stapler across the rectum. The TA stapler then is inserted into the pelvis around the rectal segment. The ureters and any lateral tissue are pushed safely away, and the stapler is fired (Fig. 43-19.2). A knife blade is used to divide the proximal end of the rectum, and the low anterior resection specimen is removed. The TA stapler is opened and passed off the field. The pelvis is irrigated, and a laparotomy sponge is left in place to tamponade any surface oozing.

FIGURE 43-19.2

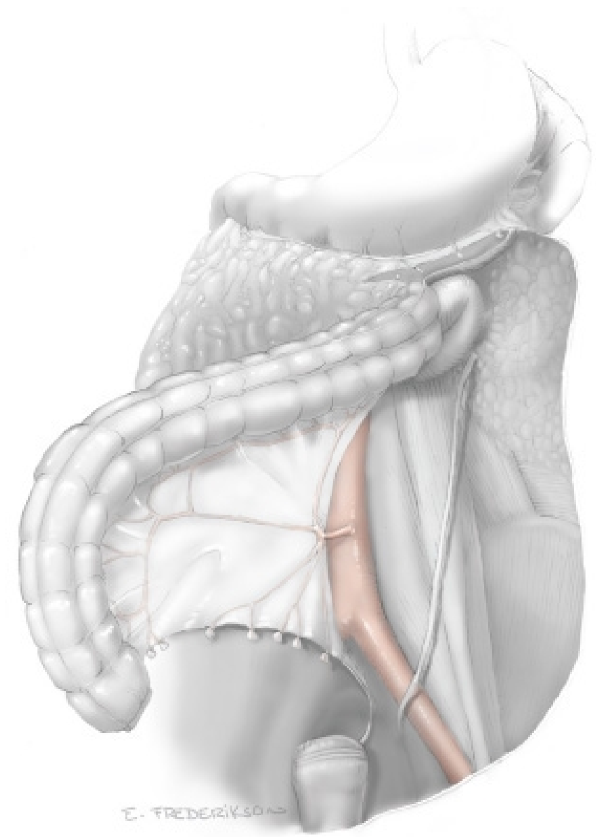


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Dividing the distal end.

8. **Mobilization.** The decision now is made to perform an anastomosis instead of an end-sigmoid colostomy (see Section 43-15, Colostomy). The upper abdominal retractors are removed, and the proximal sigmoid colon is mobilized by incising peritoneum along the white line of Toldt toward the splenic flexure. A combination of electrosurgical blade and blunt dissection typically is used. The proximal sigmoid colon is intermittently placed into the deep pelvis to assess the extent of further dissection needed to achieve a tension-free anastomosis. Ideally, the proximal sigmoid colon sits comfortably on top of the distal rectum. To achieve this, mobilization at times may encompass the splenic flexure (Fig. 43-19.3). Occasionally, the hepatic flexure may need to be mobilized also. Sufficient mobilization is critical to ensure a tension-free anastomosis.

FIGURE 43-19.3



Mobilizing the descending colon.

9. **Preparing the Anastomic Sites.** The proximal and distal stapled bowel ends now must be cleared of any fatty tissue or epiploica to allow sufficient mucosa-to-mucosa contact during anastomosis. The staple line of the proximal sigmoid is grasped with two Allis clamps at the lateral edges and elevated. Debakey forceps are used to place any surrounding fatty tissue on traction, and an electrosurgical blade is used to dissect these away from the bowel serosa. This can be particularly difficult in patients with prominent diverticulosis. A similar dissection also may be required on the distal rectal segment.

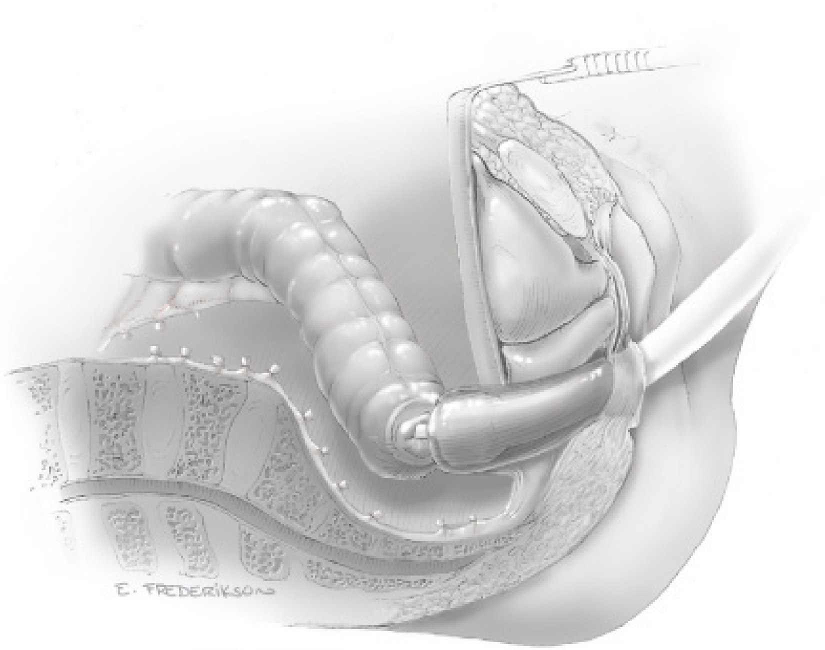
10. **Placing the Anvil.** The largest possible EEA circular stapler that will fit the bowel segments, typically 31- or 34-mm size, should be used. This provides a commodious anastomosis that will lessen the chances of symptomatic rectal stenosis. The proximal sigmoid colon again is held with Allis clamps, and scissors are used to remove the entire staple line. The Allis clamps are replaced to grasp the mucosa/serosa and hold open the proximal sigmoid. Sizing instruments may be used if necessary to decide which EEA instrument is best. The anvil is detached from the stapler, lubricated, and gentle inserted by rotating it into the proximal sigmoid. Its concave surface faces proximally, away from the anticipated anastomotic site (Fig. 43-19.4 Inset). Sequential stitches that pierce through bowel serosa, muscularis, and mucosa create a purse string around the anvil. These through-and-through stitches using 2-0 Prolene are placed 5 to 7 mm from the mucosal edge. The purse string begins and ends on the outside of the bowel serosa around the anvil spike and then is tied securely. Allis clamps are removed. Irrigation may be performed if bowel contents have spilled.

11. **Placing the Stapler.** The distal rectal stump is re-examined to ensure that all surrounding fatty tissue has been dissected

free. The surgical team then reviews the details of using an EEA instrument. The shaft is extended and spike attached. The shaft then is retracted into the instrument. The EEA is lubricated and gently inserted into the anus until the circular outline is visible and seen to be gently pressing on the rectal staple line. The wing nut is gently rotated and guided by the abdominal surgeon so that the spike tents the mucosa just posterior to the staple line. Gentle abdominal countertraction may be helpful as the spike pops through the entire bowel thickness. The shaft becomes visible, and the spike is removed with a Pean clamp.

12. **Stapling.** The abdominal surgeon lowers the proximal sigmoid to the distal rectum and connects the anvil with the EEA shaft. An audible click should be heard to confirm the placement. The tip of the EEA is held perfectly still while the wing nut is again rotated to retract the shaft back into the EEA until the handle indicator is in the correct position (Fig. 43-19.4). The safety is released, and the instrument is fired by squeezing and depressing the handles completely (incomplete squeezing can result in partial stapling). The wing nut then is turned to the specified position to release the staple line. The EEA with its attached anvil then is gently rotated and slowly removed from the rectum. The anastomosis should be visualized by the abdominal surgeon throughout the process. Distal retraction of the anastomosis or inability to remove the EEA suggests that the stapler was not completely fired. This situation may be salvaged by gently pulling the EEA through the anus and cutting inside the staple line to release the anastomosis. The anvil is removed from the EEA instrument and inspected to confirm that two completely intact circular "donuts" of rectal tissue are present.

FIGURE 43-19.4



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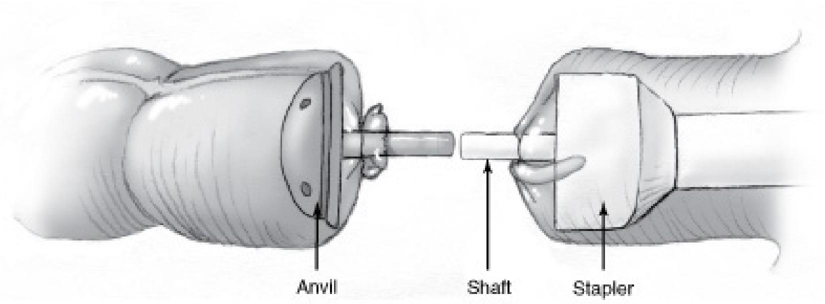
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

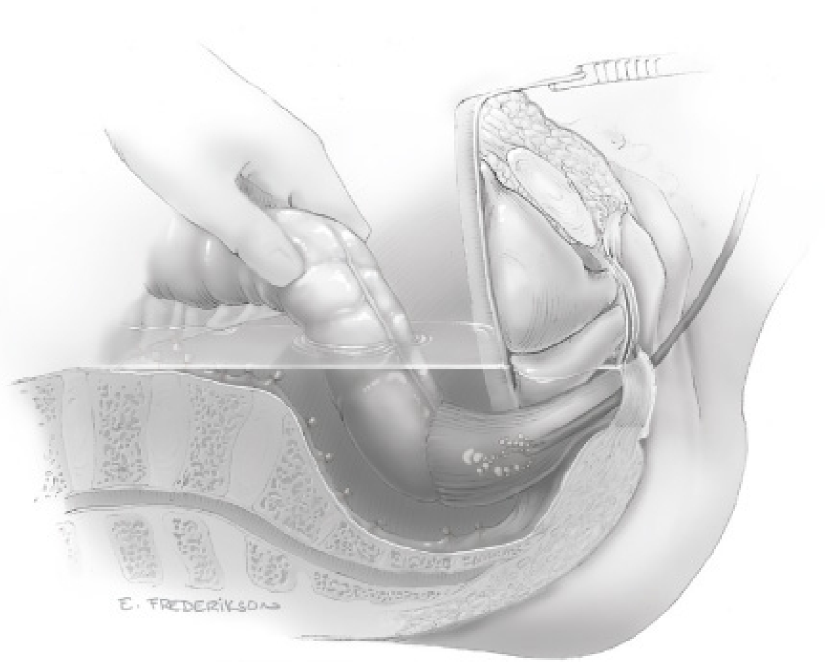


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Performing the end-to-end anastomosis.

13. **Rectal Insufflation.** Warmed saline is irrigated into the pelvis. The integrity of the anastomosis now may be checked by gently inserting a proctoscope or red rubber catheter into the anus, but distal to the anastomosis, and insufflating air. The abdominal surgeon should gently palpate the sigmoid to make certain that air is entering the sigmoid proximal to the anastomotic site. No air bubbles should be visible when the connection is watertight (Fig. 43-19.5). The appearance of bubbles suggests a leak, but this should be double-checked for authenticity. Occasionally, air is being erroneously pumped into the vagina owing to incorrect placement. If there is any valid suspicion for a leak, the distal rectum should be divided again with the TA stapler and the anastomosis redone. Diverting colostomy also may be considered if the problem cannot be managed otherwise.

FIGURE 43-19.5



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Testing the anastomosis.

14. **Final Steps.** All pedicle sites should be rechecked for hemostasis and the pelvis irrigated. Nasogastric suction is not required routinely. In addition, suction drainage does not necessarily improve outcome or influence the severity of complications. (Merad, 1999).

Postoperative

The most common early postoperative complications are similar to those of other major abdominal operations and include fever, ileus, wound separation, and anemia requiring transfusion. Serious events such as bowel obstruction and fistula should develop infrequently (Gillette-Cloven, 2001). Long term, many patients will have a poor functional result, including fecal incontinence or chronic constipation (Rasmussen, 2003).

Low rectal anastomoses have much higher leak rates than intraperitoneal large bowel anastomoses. Occasionally, this complication can be managed successfully with percutaneous drainage and bowel rest. Otherwise, a diverting colostomy may be required. Risk factors for postoperative leakage include previous pelvic irradiation, diabetes mellitus, low preoperative serum albumin, surgical duration, and a low anastomosis (≤6 cm from the anal verge) (Matthiessen, 2004; Mirhashemi, 2000; Richardson, 2006). Other potential causes are technical missteps or inadequate bowel preparation. Suction drainage may prevent some leaks by removing blood, serum, and cellular dÃ©bris as a culture medium but also can impair healing if placed too close to the anastomotic site (Hirsch, 1997; Vignali, 1997).

43-20 INTESTINAL BYPASS

This bowel anastomotic procedure typically connects a section of the ileum to the ascending or transverse colon and thereby "bypasses" a portion of diseased bowel. Following anastomosis, the closed, bypassed small bowel segment remains.

There are relatively few indications for intestinal bypass in gynecologic oncology, and this procedure accounts for only approximately 5 percent of all bowel operations performed for these cancers (Barnhill, 1991). In all circumstances, removal of diseased bowel and end-to-end anastomosis are preferable (Hoskins, 1987). However, some patients will have unresectable tumor, dense adhesions, extensive radiation injury, or other factors that prohibit this. In these patients, a poor decision to perform an aggressive dissection can result in numerous enterotomies, hemorrhage, or other intraoperative catastrophies with major postoperative sequelae. Instead, an intestinal bypass can be performed quickly with minimal morbidity. Many times a bypass is selected because it is the easiest palliative maneuver for a terminally ill patient. The main purpose is to re-establish an adequate bowel communication to relieve an obstruction and regain the ability to take oral nourishment.

Preoperative

PATIENT EVALUATION

The intestinal tract should be evaluated carefully by an upper gastrointestinal (GI) radiologic series with small bowel follow-through and/or computed tomographic (CT) scanning. Invariably, radiation injuries are located at the terminal ileum, but there may be complex fistulas or multiple sites of obstruction to be addressed. In most circumstances in which a bypass is considered, the surgeon should anticipate limitations in exploring the abdomen adequately intraoperatively. Careful analysis of preoperative findings will help to ensure that bypass encompasses the entire lesion and does not leave a distal obstruction.

CONSENT

Patients usually have a miserable quality of life when bypass is considered, and the operation's main goal is to improve patient symptoms. The counseling process should emphasize that intraoperative judgment will dictate whether a small bowel resection, ileostomy, large bowel resection, colostomy, or bypass is indicated. Many risks are similar to those of other intestinal surgical procedures and include anastomotic leaks, obstruction, abscess formation, and fistula. Blind loop syndrome, discussed later, is one long-term complication that is characteristic to the bypass procedure.

PATIENT PREPARATION

To minimize fecal contamination during bowel incision, aggressive bowel preparation such as with a polyethylene glycol with electrolyte solution (GoLYTELY) is performed the day prior to surgery unless contraindicated, such as with bowel obstruction or perforation. Additionally, broad-spectrum antibiotics are given perioperatively because of the possibility of stool contamination. If a prolonged recovery is anticipated, total parenteral nutrition should be considered.

Intraoperative

INSTRUMENTS

To prepare for complicated resections, bowel staplers such as an end-to-end anastomosis (EEA), gastrointestinal anastomosis (GIA), and transverse anastomosis (TA) staplers should be available.

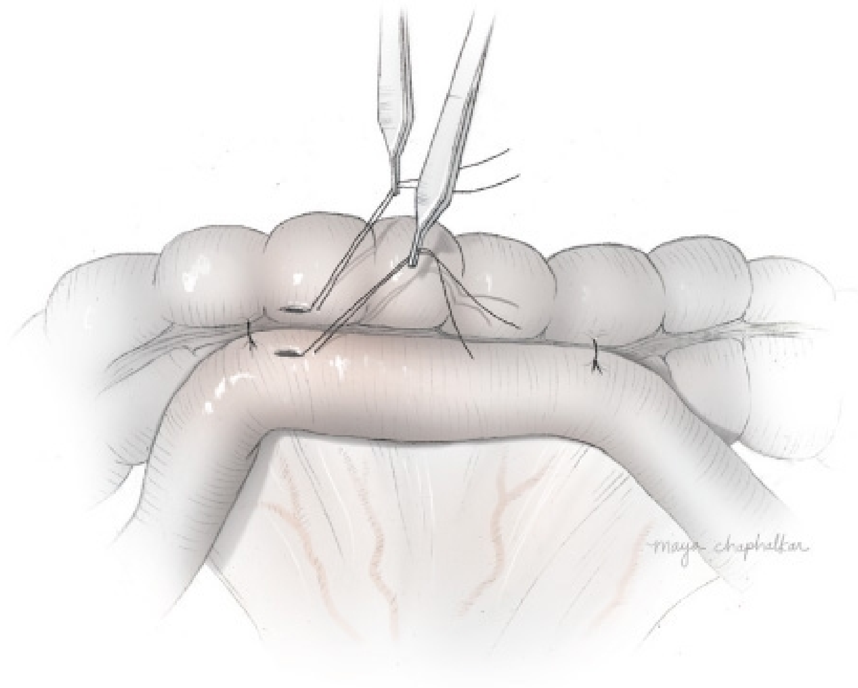
Surgical Steps

1. **Anesthesia and Patient Positioning.** Bypass is performed under general anesthesia with the patient positioned supine. Prior to surgery, the abdomen is surgically prepared, and a Foley catheter is inserted.

2. **Abdominal Entry and Exploration.** Intestinal bypass generally requires a midline vertical incision for adequate exposure. The surgeon should explore the entire abdomen first to identify bowel lesions. In addition, the remaining bowel should be examined to exclude other obstructive sites. Healthy-appearing bowel proximal and distal to the lesion is selected with the intent of preserving the maximal amount of intestine. Typically, the bypass will entail connecting a section of the ileum to the ascending or transverse colon.

3. **Aligning the Bowel.** The two bowel segments selected for the anastomosis are aligned side-to-side without tension or twisting. The hepatic or splenic flexure of the transverse colon may require mobilization from its peritoneal attachments to achieve a tension-free connection. The bowel segments are held in position with 2-0 silk stay sutures about 6 cm apart on the antimesenteric border. Two Adson forceps are used to hold up the small bowel serosa laterally and transversely on traction. An electrosurgical blade is used to enter the bowel lumen on its antimesenteric surface (Fig. 43-20.1). The same maneuver is performed on the tenia coli to enter the colon.

FIGURE 43-20.1

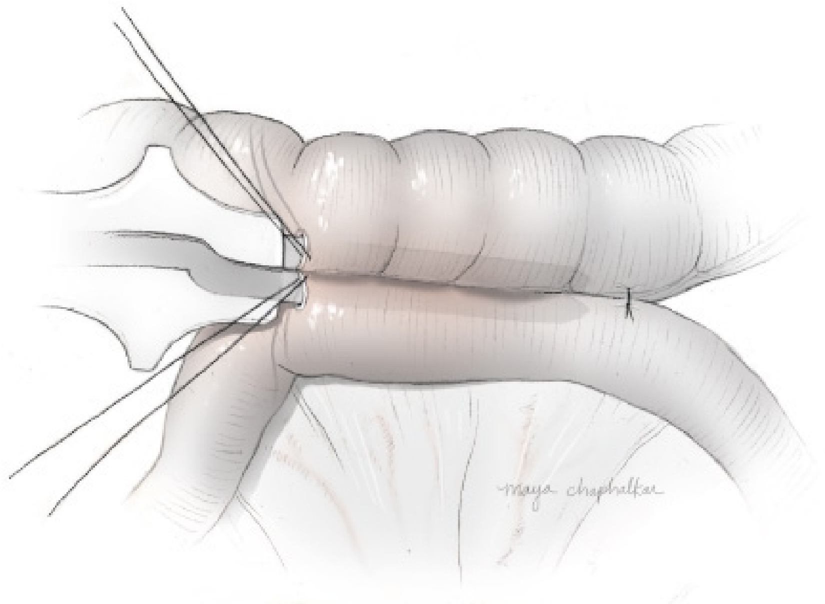


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Aligning the bowel.

4. **Performing the Side-to-Side Anastomosis.** One fork of the GIA stapler is inserted into each bowel segment lumen. The bowel is adjusted, if necessary, to position the antimesenteric surfaces between the stapler forks. The stapler then is closed and fired (Fig. 43-20.2). The remaining open defect then can be closed with the TA stapler and the excess bowel trimmed.

FIGURE 43-20.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Performing the side-to-side anastomosis.

5. **Final Steps.** Occasionally, small bleeding sites will be coagulated electrosurgically on the staple line. The anastomosis also should be palpated to verify an adequate lumen. The bowel should be re-examined to make certain that the connection is watertight and that there is no tension on the anastomosis.

Postoperative

Recovery after bypass surgery should be rapid compared with that following a large resection with anastomosis. In general, a postoperative ileus will resolve in several days, and patients may begin oral alimentation. The underlying clinical situation prompting the need for bypass surgery will dictate most of the clinical course. Relatively minor complications such as fever and wound infection or separation occur commonly. Fistulas, obstruction, anastomotic leaks, abscesses, peritonitis, and perforation are more difficult to manage and often lead to a prolonged postoperative course or death.

Blind loop syndrome is a condition of vitamin B_{12} malabsorption, steatorrhea, and bacterial overgrowth of the small intestine. The usual scenario is a bypass procedure that leaves a segment of nonfunctional, severely irradiated bowel behind. Stasis of the intestinal contents leads to dilatation and mucosal inflammation. Symptoms resemble a partial small bowel obstruction and include nausea, vomiting, diarrhea, bloating, abdominal distention, and pain. Bowel perforation is possible.

Antibiotics often will alleviate the condition, but recolonization and resumption of the blind loop syndrome are common (Swan, 1974). The only definitive therapy for recurrent episodes is exploration with resection of the bypassed segment. To avoid this syndrome, a surgeon may intraoperatively divide the bowel proximal and distal to the lesion and perform a side-to-side anastomosis. The closed loop can be relieved by creation of a mucus fistula at the abdominal wall.

43-21 APPENDECTOMY

Removal of the appendix may be indicated during gynecologic surgery for a variety of reasons. The need, however, is commonly not recognized until an operation is already underway because signs and symptoms of a number of benign gynecologic conditions can mimic appendicitis (Bowling, 2006; Fayez, 1995; Stefanidis, 1999).

In addition, malignancies may involve the appendix. Ovarian cancer frequently metastasizes to the appendix and thereby warrants removal (Ayhan, 2005; Fontanelli, 1992). Primary tumors of the appendix are rare but commonly metastasize to the ovaries (Gehrig, 2002). Pseudomyxoma peritonei is the classic type of mucinous tumor of appendiceal origin that spreads to the ovaries and may implant throughout the abdomen (Prayson, 1994).

Elective coincidental appendectomy is defined as the removal of an appendix at the time of another surgical procedure unrelated to appreciable appendiceal pathology. Possible benefits include preventing a future emergency appendectomy and excluding appendicitis in patients with chronic pelvic pain or endometriosis. Other groups that may benefit include women in whom pelvic or abdominal radiation or chemotherapy is anticipated, women undergoing extensive pelvic or abdominal surgery in which major adhesions are anticipated postoperatively, and patients such as the developmentally disabled in whom making the diagnosis of appendicitis may be difficult because of diminished ability to perceive or communicate symptoms (American College of Obstetricians and Gynecologists, 2005). Most studies suggest that there is little, if any, increased morbidity associated with elective coincidental appendectomy at the time of gynecologic surgery, whether performed during laparotomy or during laparoscopy (Salom, 2003).

Preoperative

Specific preoperative tests or preparations are not required prior to appendectomy. In general, the consenting process for gynecologic surgery should include a discussion of possible "other indicated procedures" such as appendectomy when anticipated intraoperative findings and the potential for performing an appendectomy are uncertain.

There is a small increased risk of nonfatal complications associated with appendectomy (American College of Obstetricians and Gynecologists, 2005). Hematoma formation at the mesoappendix may cause an ileus or partial small bowel obstruction. Perforation of the stump is rare and typically follows insecure suture placement.

Intraoperative

Surgical Steps

1. **Anesthesia and Patient Positioning.** Appendectomy is performed under general anesthesia in the supine position. Postoperative hospitalization is individualized and depends on concurrent surgeries and associated clinical symptoms.

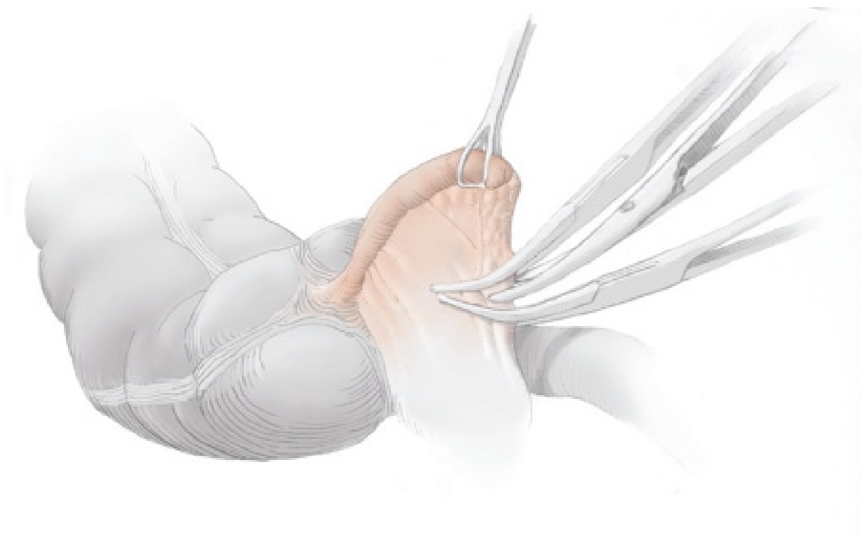
2. **Abdominal Entry.** Appendectomy can be performed through almost any incision. A laparoscopic approach or an oblique McBurney incision in the right lower quadrant of the abdomen traditionally is selected for appendectomy. However, in gynecologic cases, the needs of planned concurrent procedures commonly will dictate incision choice.

3. **Locating the Appendix.** The appendix is located by first grasping the cecum and gently elevating it upward into the incision. Insertion of the terminal ileum should be visible, and the appendix typically is obvious at this point. Infrequently, an appendix is retrocecal or otherwise difficult to identify. In this situation, the convergence of the three teniae coli can be followed to locate the appendiceal base.

4. **Mesoappendix Division.** The appendix tip is elevated with a Babcock clamp, and the cecum is held laterally to place the mesoappendix on gentle traction. The appendiceal artery usually is very difficult to distinguish reliably because of abundant surrounding fatty tissue. Thus, curved hemostats are used to successively clamp the mesoappendix and its vessels to reach the appendiceal base (Fig. 43-21.1).

   The first hemostat is placed horizontallyâ€”aiming directly toward the base of the appendix. The second hemostat is placed at a 30-degree angle so that the tips meet but Metzenbaum scissors have room to cut between the two clamps. The mesoappendix pedicle is ligated with 3-0 delayed-absorbable suture. This step typically is repeated once or twice to comfortably reach the base of the appendix.

FIGURE 43-21.1



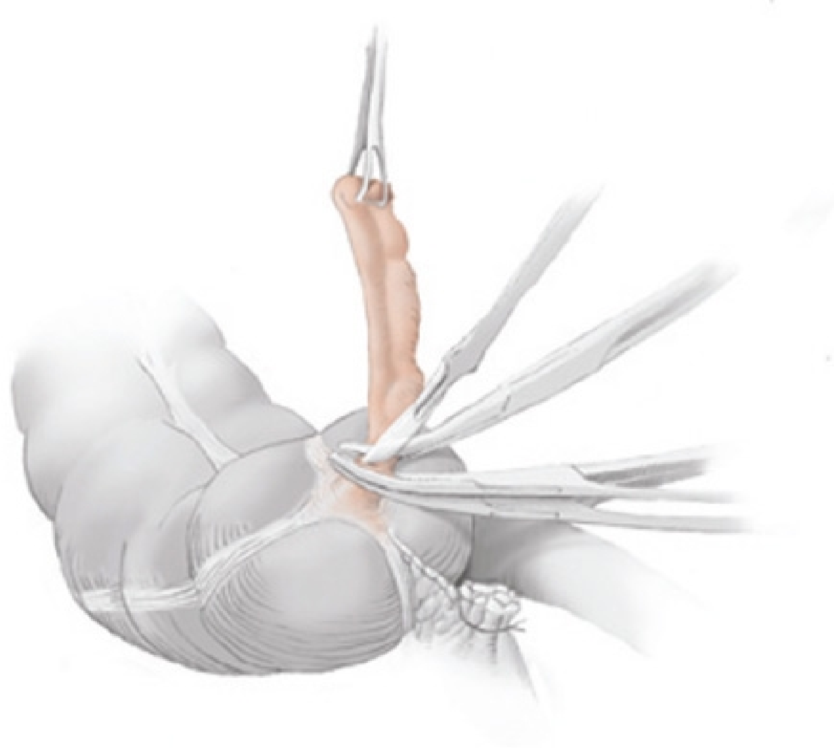
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Clamping the mesoappendix.

5. **Appendix Ligation.** At this point, the appendix has been isolated completely from the mesoappendix and is still held vertically by a Babcock clamp. A first hemostat is placed at the appendiceal base, and a second is positioned directly above (Fig. 43-21.2). A third hemostat is closed with a few millimeters of intervening tissue to allow for passage of a knife blade. The knife then cuts between the second and third clamps, and the appendix is removed. The "contaminated" knife and appendix then are handed off the field.

   A 2-0 silk suture is placed beneath the first hemostat with removal of that clamp. A separate suture is placed underneath the second hemostat for added security of the appendiceal stump. Gentle electrosurgical coagulation at the stump surface also may be performed.

FIGURE 43-21.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Ligation of the appendix.

6. **Final Steps.** There is no need to invert the stump or to place a purse-string suture around it. The cecum may be returned to the abdomen and remaining concurrent surgeries completed.

Postoperative

Patient care postoperatively is dictated by other surgeries performed. Delayed initiation of oral intake or administration of additional antibiotics is not required for appendectomy alone.

43-22 RADICAL PARTIAL VULVECTOMY

To reduce the high morbidity of curative surgery for vulvar cancer without sacrificing cure, a less extensive resection than complete radical vulvectomy may be used. Women with well-localized, unifocal, clinical stage I invasive lesions are ideal candidates (Stehman, 1992). *Radical partial vulvectomy* is a somewhat ambiguously defined operation. It generally refers to complete removal of the tumor-containing portion of the vulvaâ€”wherever it is locatedâ€—with 1- to 3-cm skin margins and excision to the *perineal membrane* . This membrane was previously termed the inferior fascia of the urogenital diaphragm and may also be referred to as the deep perineal fascia. *Radical hemivulvectomy* refers to a larger resection that may be anterior, posterior, right, or left.

The chief concern in performing a less extensive operation for vulvar cancer is the possibility of an increased risk of local recurrence from multifocal disease. However, survival after partial or complete radical vulvectomy is comparable if negative margins are obtained (Farias-Eisner, 1994; Lin, 1992; Scheistroen, 2002). Following less aggressive surgical resection, 10 percent of patients will develop a recurrence at the ipsilateral vulva, and this may be treated by re-excision (Desimone, 2007).

Preoperative

PATIENT EVALUATION

Biopsy confirmation of invasive cancer is an obvious necessity. Squamous lesions with less than 1 mm of invasion may be managed adequately with only wide local excision (see Chap. 31, Lymphatic Vascular Space Invasion). In general, patients undergoing radical partial vulvectomy should not require reconstructive grafts or flaps to cover operative defects.

CONSENT

Morbidity after radical vulvar surgery is common. Wound separation or cellulitis develops frequently. Long-term changes may include displacement of the urine stream, dyspareunia, vulvar pain, and sexual dysfunction. Surgeons should be sensitive to these possible sequelae and counsel the patient appropriately, emphasizing the curative intent and limited scope of the operation.

PATIENT PREPARATION

Bowel preparation may be indicated with posteriorly located resections.

Intraoperative

Surgical Steps

1. **Anesthesia and Patient Positioning.** Radical partial vulvectomy has been performed under local anesthesia combined with sedation in medically compromised patients (Manahan, 1997). However, regional or general anesthesia typically is required.

   Inguinal lymphadenectomy (see Section 43-24, Inguinal Lymphadenectomy) typically is performed before vulvar resection. Patients then may be repositioned to provide full exposure to the vulva, and the vulva is surgically prepared.

2. **Radical Partial Vulvectomy: Variations.** The area of tissue to be removed when radically excising a small cancer depends on the size and location of the tumor (Fig. 43-22.1). The dotted line indicates a planned skin incision for: (*A*) a 1-cm right labia majora tumor and planned 2-cm surgical margins; (*B*) a 2.5-cm periclitoral tumor, which requires an anterior hemivulvectomy; and (*C*) a 2.5-cm midline posterior fourchette tumor requiring posterior hemivulvectomy.

FIGURE 43-22.1

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

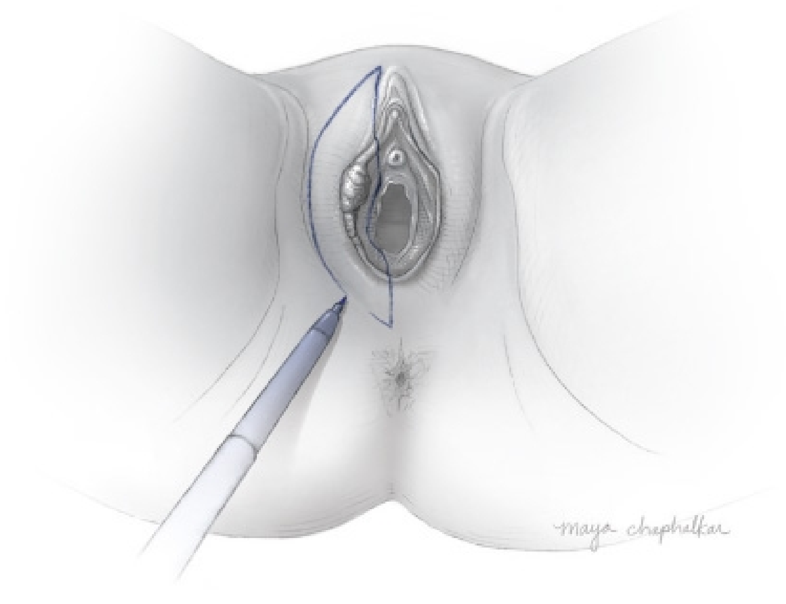
Partial radical vulvectomy: variations.

3. **Right Hemivulvectomy: Making the Lateral Incision.** The planned excision is drawn on the vulva with a surgical

marking pen to provide 2-cm margins (Fig. 43-22.2). Tapering the incision anteriorly and posteriorly will aid a tension-free closure. The lateral skin incision is made with a knife (no. 15 blade) into the skin and subcutaneous fat.

Forceps are used to place the skin edges on traction and aid electrosurgical dissection downward and lateral until reaching the perineal membrane (Fig. 43-22.3). An index finger then can be used to develop the plane between the fat pad of the labia majora and the subcutaneous tissue of the lateral thigh.

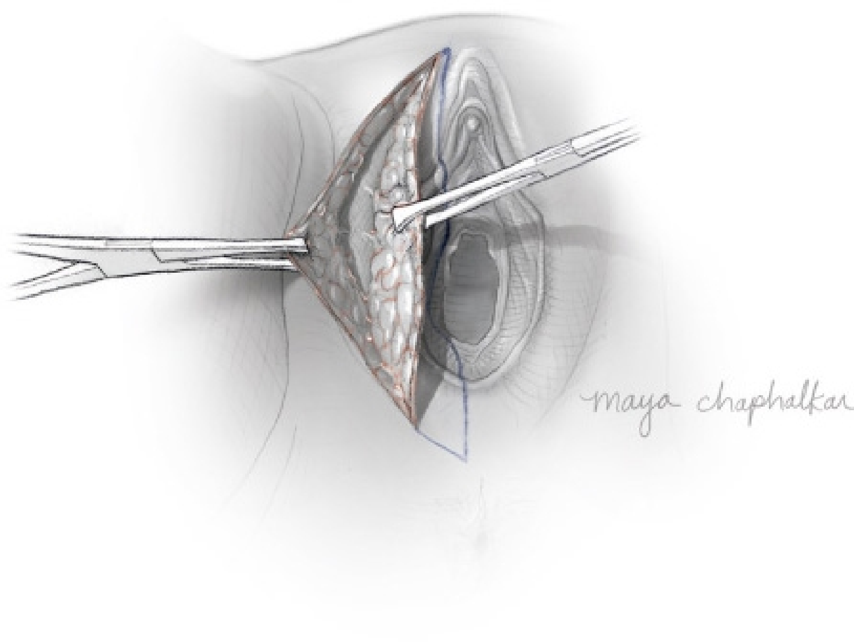
FIGURE 43-22.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Right hemivulvectomy: outlining the skin incision.

FIGURE 43-22.3

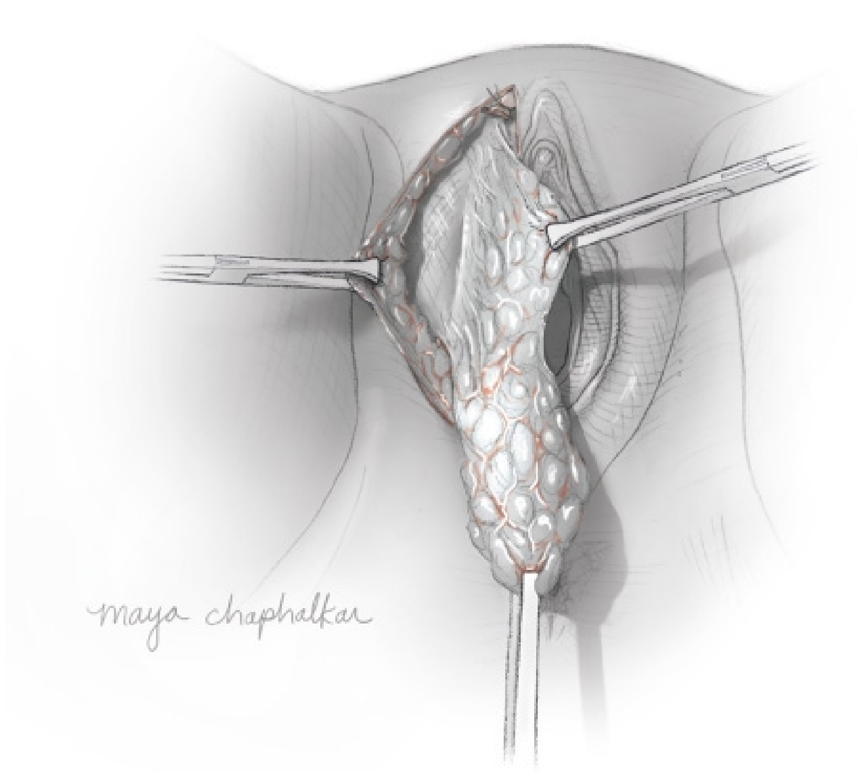


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Right hemivulvectomy: lateral dissection to the fascia lata.

4. **Right Hemivulvectomy: Completing the Resection.** The lateral plane that has been developed is extended medially by blunt and electrosurgical dissection along the perineal membrane. The skin edge of the specimen then is placed on lateral traction, and the medial (vaginal mucosa) incision is incised from anterior to posterior. The labial fat pad is transected anteriorly, and the entire radical right hemivulvectomy specimen is placed on downward traction to aid final dissection along the mucosal incision in an anterior-to-posterior direction (Fig. 43-22.4). The specimen is marked at 12 o'clock and examined to ensure adequate margins.

FIGURE 43-22.4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Right hemivulvectomy: removal of the specimen.

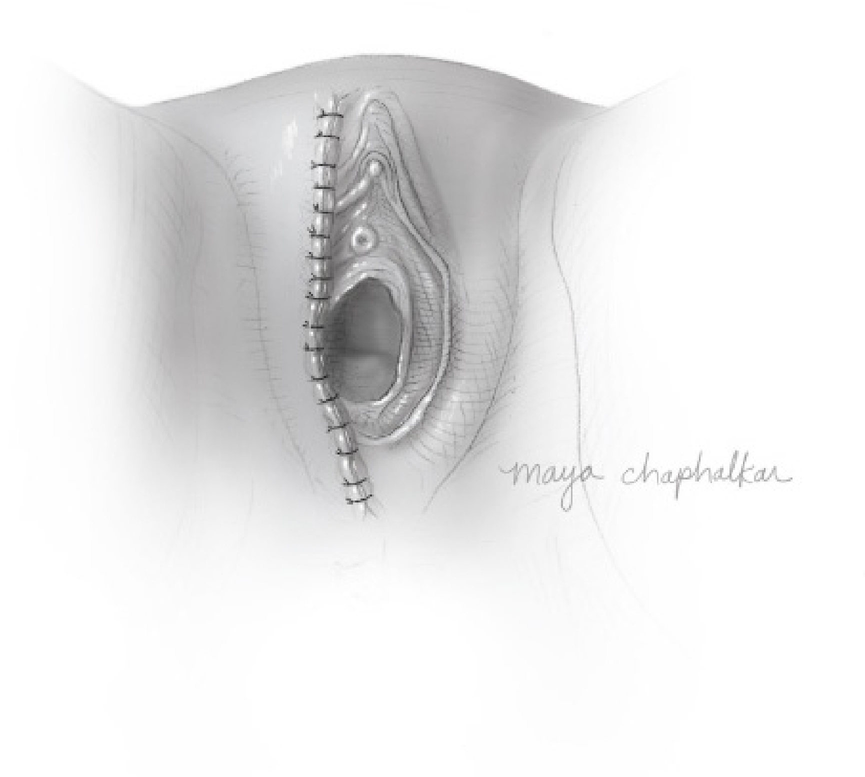
5. **Right Hemivulvectomy Closing the Defect.** A gauze sponge may be held firmly in the cavity and rolled downward to guide the electrosurgical blade in achieving hemostasis. The defect then can be irrigated and evaluated to determine requirement for a tension-free closure while minimizing anatomic distortion (Fig. 43-22.5). Several pedicles are visible, particularly at the vaginal margin, where vessels were clamped and tied. In general, lateral undermining of the subcutaneous tissue will provide sufficient mobility to allow primary closure. Interrupted delayed-absorbable sutures are used to create a layered re-approximation of deeper tissues. Interrupted vertical mattress sutures with knots placed laterally are used to close the skin (Fig. 43-22.6).

FIGURE 43-22.5

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Right hemivulvectomy: evaluation of the surgical defect.

FIGURE 43-22.6



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Right hemivulvectomy: closure of the surgical defect.

6. **Anterior Hemivulvectomy.** This variation requires removal of the clitoris and partial resection of the labia minora, labia majora, and mons pubis. The most anterior portion of the incision is created first on the mons and carried down to the aponeurosis over the pubic symphysis. The specimen is reflected posteriorly to guide dissection. In the midline, the clitoral vessels are clamped and divided separately. The posterior incision is made above the urethral meatus with careful attention to Foley catheter location to avoid urethral injury. Layers of interrupted delayed-absorbable sutures are used to close the defect. Usually, the area surrounding the urethral meatus should be left to granulate secondarily.

7. **Posterior Hemivulvectomy.** This variation entails removal of a portion of the labia majora, Bartholin glands, and upper perineal body. It is generally necessary to compromise the deep margin in this resection because of anal sphincter and rectum proximity. The skin is first incised posteriorly, and a finger is placed into the rectum to guide proximal dissection. The specimen is retracted upward gradually off the sphincter. Dissection proceeds laterally until the anterior margin at the introitus can be incised to complete the resection. The perineal body will need to be re-inforced with interrupted sutures of delayed-absorbable material to provide bulk and to allow re-approximation of skin edges for a tension-free closure. Rectal examination should be performed at the end of surgery to confirm the absence of stitches or stenosis. Incontinence of flatus or stool may develop postoperatively despite efforts to preserve the sphincter.

8. **Partial Urethral Resection (Optional).** If an anterior lesion encroaches on the urethral meatus, then a distal urethrectomy may be required to achieve a cancer-free margin. Radical partial vulvectomy otherwise should be completed almost entirely. The urethra may be transected anywhere distal to the pubic arch. The length of resection is measured first against the Foley catheter. The meatus is held with an Allis clamp, and the specimen is placed on traction. The posterior urethra is incised with a knife, and the underlying mucosa is sewn to the adjacent wall with 4-0 delayed-absorbable suture at the 6 o'clock position. The urethral incision is extended laterally with additional sutures at 3 and 9 o'clock until the proximal portion of the Foley can be transected and removed from the bladder. The transection is completed, and a final stitch is placed at 12 o'clock.

Partial or total urinary incontinence may be alleviated somewhat by urethral plication in some cases.

9. **Final Steps.** Suction drains typically are not required but should be at least considered in some circumstances. Copious irrigation is indicated at various times during closure of the defect to minimize infection postoperatively. No formal dressing is applied at the end of surgery. However, fluffed-out gauze may be placed at the perineum and held in place with mesh underwear to tamponade any subcutaneous bleeding and to promote a clean and dry operative site in the immediate postoperative period.

Postoperative

Meticulous care of the vulvar wound is mandatory to prevent morbidity. The vulva should be kept dry by use of a blow dryer or fan. Within a few days, brief sitz baths or bedside irrigation followed by air drying will help to keep the incision clean. Patients should be instructed not to wear underwear in the hospital. Discharge instructions also should encourage loose-fitting gowns to aid healing and efforts to minimize wound tension.

Incision separation is the most common postoperative complication and often will involve only a portion of the incision (Burke, 1995). The wound should be dÃ©brided if necessary, and efforts to keep the site clean and dry are continued. Granulation tissue eventually will allow healing by secondary intention, but recovery time will be extended significantly.

Sexual dysfunction may relate to a sense of disfigurement. Scarring also may result in discomfort or an alteration in sensation that affects a woman's sexual satisfaction. Sensitivity to these concerns will enable a dialogue to develop that can lead to possible management options.

43-23 RADICAL COMPLETE VULVECTOMY

If cancers are so extensive that no meaningful portion of the vulva can be preserved, radical complete vulvectomy is indicated over the more limited procedureâ€"radical partial vulvectomy. The operation typically is performed through three separate incisions: one each for the vulvectomy and bilateral inguinal lymphadenectomy. Intact skin lies between these incisions to aid wound healing. The en bloc incision, colloquially termed the *butterfly* or *longhorn* incision, was used traditionally to remove these skin bridges and the underlying lymphatic channels that potentially harbored "in transit" tumor emboli (see Fig. 31-5A). (Gleeson, 1994). However, such recurrences are rare, and the en bloc technique largely has been abandoned (Rose, 1999). Thus, the three-incision procedure is preferred because survival rates are equivalent and major morbidity is reduced dramatically (Helm, 1992)

Removal of an entire vulvar lesion with an adequate 2-cm margin usually creates a large surgical defect. In some cases, wound margins may be closed primarily without tension by undermining and mobilizing adjacent tissues. On other occasions, a split-thickness skin graft, lateral skin transposition, rhomboid flap, or other reconstructive procedure will be indicated to reduce the chances of wound separation (see Section 43-26, Reconstructive Grafts and Flaps).

Preoperative

PATIENT EVALUATION

Biopsy confirmation of invasive cancer should precede surgery. Confluent squamous lesions with less than 1 mm of invasion may be managed adequately by skinning vulvectomy (see Section 43-25, Skinning Vulvectomy). Depending on the location of the tumor, the clitoral-sparing modification of radical complete vulvectomy also is an option (Chan, 2004). Frequently, patients are elderly, obese, or have significant coexisting medical problems that must be considered.

CONSENT

Major morbidity is common soon after radical complete vulvectomy, and partial wound separation or cellulitis occurs frequently. Complete wound breakdown is more problematic, and weeks of aggressive hospital care may be required to promote secondary healing. Premature hospital discharge may result in poor home wound care. Resulting tissue necrosis often requires re-admission and surgical dÃ©bridement.

Long-term changes may include displacement of the urine stream, dyspareunia, vulvar pain, and sexual dysfunction. Accordingly,

surgeons should be aware of possible sequelae and counsel appropriately. Emphasis is placed on the curative intent of the operation and the need for adequate tumor-free margins to lessen local recurrence risks.

PATIENT PREPARATION

Bowel preparation may be indicated with posteriorly located lesions. Antibiotic prophylaxis has not been shown to reduce wound infection or breakdown (Hopkins, 1993).

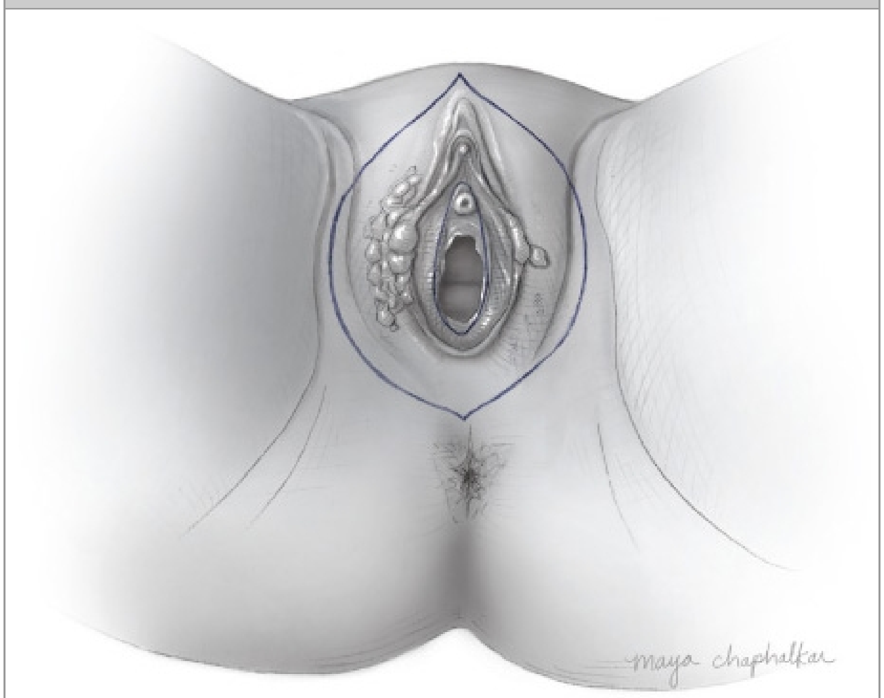
Intraoperative

Surgical Steps

1. **Anesthesia and Patient Positioning.** Regional or general anesthesia is required, and inguinal lymphadenectomy is performed first (see Section 43-24, Inguinal Lymphadenectomy). The patient then is placed in dorsal lithotomy position. Exposure and surgical preparation of the operative field should be planned to accommodate resection and reconstruction.

2. **Planning the Skin Incision.** The medial and lateral incisions are drawn to encompass the tumor and provide a 2-cm margin around the tumor. The clitoris is included if necessary. Tapering the incision anteriorly and posteriorly also will aid a tension-free closure (Fig. 43-23.1).

FIGURE 43-23.1



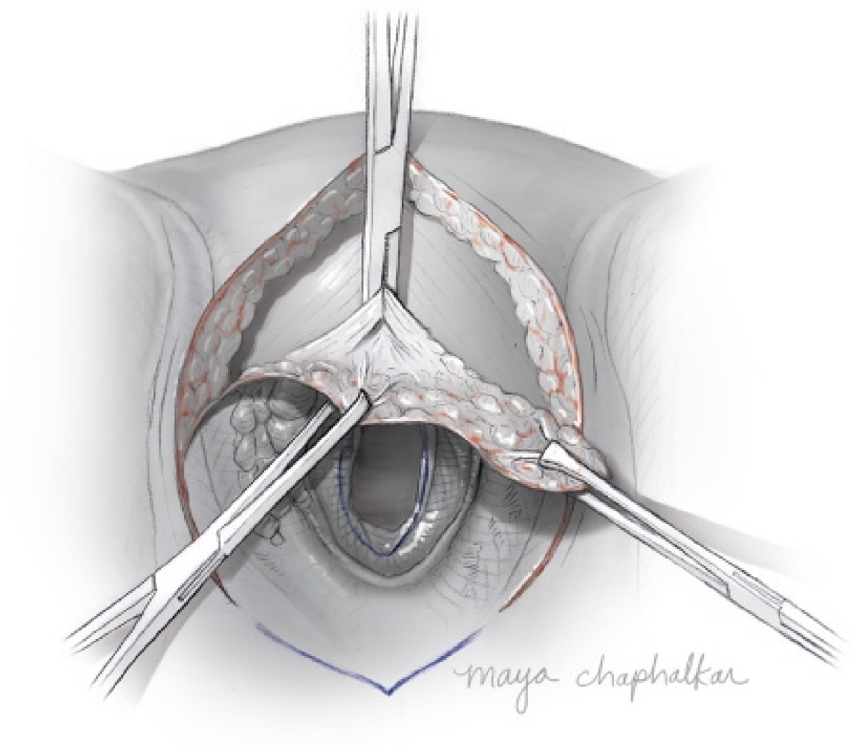
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Incisions.

3. **Anterior Dissection.** The skin incision begins anteriorly with the knife (no. 15 blade) cutting into the subcutaneous fat. The incision is extended downward about three quarters of its length. The remainder of the posterior incision is completed later to decrease bleeding. Much of the anterior dissection is described in the preceding section on radical partial vulvectomy (see Section 43-22, Radical Partial Vulvectomy, Step 6). Briefly, the incision is carried down to the pubic aponeurosis. The

specimen is reflected downward on traction to guide dissection. The vascular base of the clitoris is clamped in the midline, transected, and suture ligated with delayed-absorbable suture (Fig. 43-23.2). Electrosurgical dissection then proceeds dorsally off the pubic bone until the medial incision line is reached anteriorly. The medial incision is made above the urethral meatus to avoid injury to the urethra unless a distal urethrectomy is required (see Section 43-22, Radical Partial Vulvectomy, Step 8).

FIGURE 43-23.2

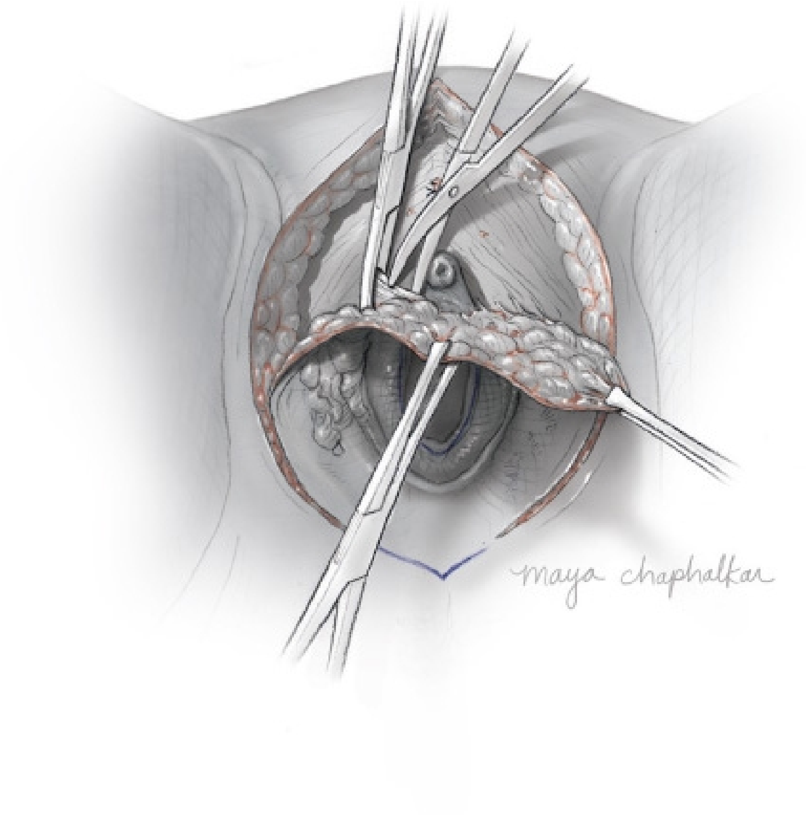


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Anterior dissection.

4. **Lateral Dissection.** Blunt finger dissection is performed to establish a plane lateral to the labial fat pads along the perineal membrane. The vulvectomy specimen is placed on traction to guide electrosurgical dissection medially to reach the vaginal wall. Vascular vestibular tissue along the sides of the vagina will need to be clamped, cut, and ligated to reduce bleeding (Fig. 43-23.3).

FIGURE 43-23.3

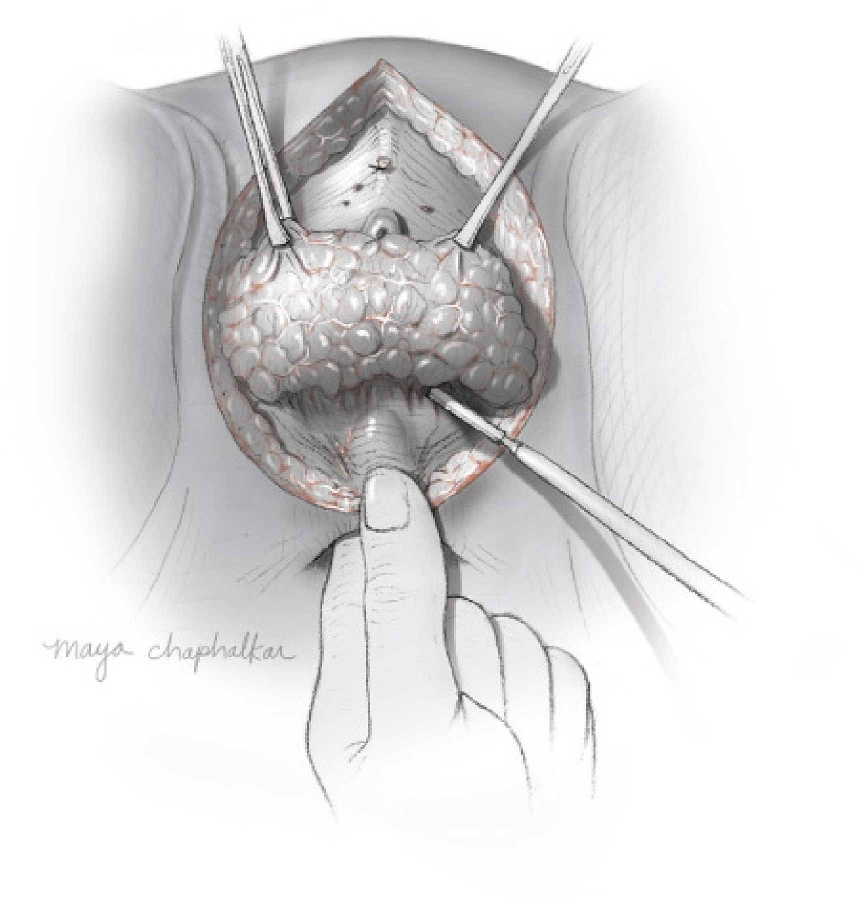


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Medial dissection.

5. **Posterior Dissection.** The outer skin incision is completed with a knife as the vulvectomy proceeds posteriorly. A finger then is placed into the rectum to prevent inadvertent injury, and the specimen now is held upward on traction. Electrosurgical dissection extends the outer incisions along the perineal membrane to the midline. The dissection continues anteriorly away from the anus until the medial incision can be made to detach the radical complete vulvectomy specimen (Fig. 43-23.4).

FIGURE 43-23.4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Posterior dissection.

6. **Evaluating the Specimen.** A stitch is placed at 12 o'clock on the specimen to orient the pathologist. Skin retraction of the specimen will make it appear narrower. However, it should be inspected carefully to assess its margins. Additional lateral or medial tissue margins can be sent separately if necessary. Alternatively, a frozen section analysis can be requested to evaluate an equivocal margin.

7. **Closing the Defect.** The wound is copiously irrigated, and hemostasis is achieved with a combination of electrosurgical coagulation, clamping, and suturing. The defect then is evaluated to determine the best method of closure (Fig. 43-23.5).

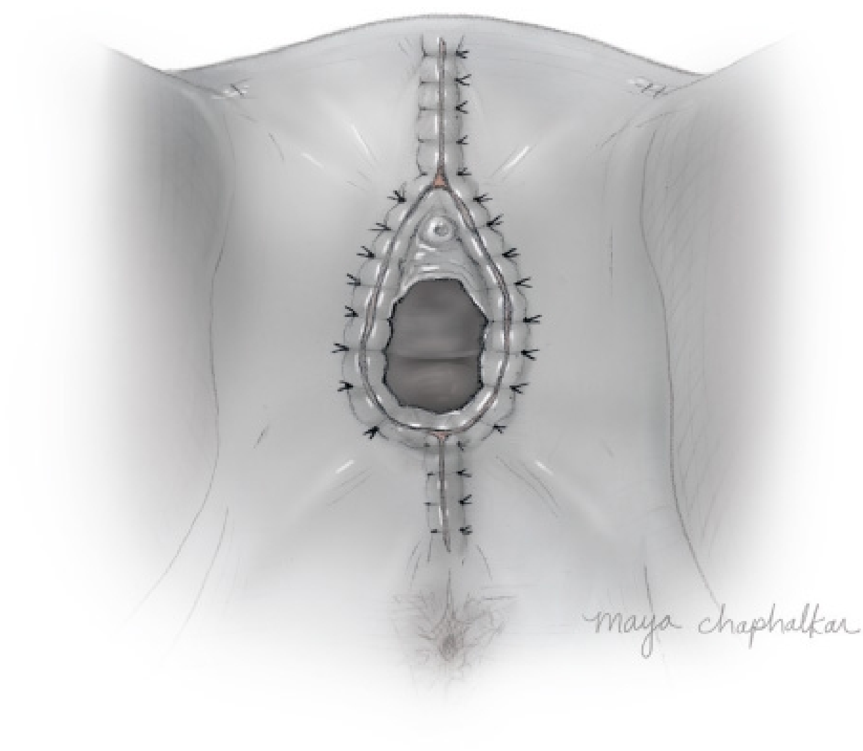
   Undermining lateral tissues will aid a tension-free primary closure. Deeper tissues are first re-approximated with interrupted delayed-absorbable suture. The vulvar skin then is closed with vertical mattress stitches using delayed-absorbable suture (Fig. 43-23.6). No stitches are placed between the skin and urethra if this displaces the urethra or creates tension on it. In such cases, this area will heal secondarily by granulation.

FIGURE 43-23.5

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Surgical defect.

FIGURE 43-23.6



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Simple closure.

8. **Final Steps.** Suction drains do not prevent wound infection or breakdown but may be considered in some cases if there is a large defect (Hopkins, 1993). If primary closure is performed, then fluffed-out gauze may be placed at the perineum and held in place with mesh underwear to keep the operative site clean and dry in the immediate postoperative period.

Postoperative

If a primary closure is performed, postoperative care is essentially the same as described for patients undergoing radical partial vulvectomy (see Section 43-22, Radical Partial Vulvectomy). Because of a larger operative defect, the likelihood of morbidity is increased correspondingly. Management of reconstructive grafts and flaps is reviewed in Section 43-26, Reconstructive Grafts and Flaps.

43-24 INGUINAL LYMPHADENECTOMY

The main indication for removal of groin nodes is staging surgery for vulvar cancer. Inguinal metastases are the most significant prognostic factor in vulvar squamous cancer, and their detection requires additional therapy (see Chap. 31, Lymphadenectomy) (Homesley, 1991). However, the utility of this dissection is more controversial in the management of vulvar malignant melanoma, and the presence of positive nodes generally is only of prognostic value. Lastly, in women with ovarian or uterine cancer, suspicion of inguinal metastases will prompt removal.

The proper extent of an inguinal lymphadenectomy for vulvar cancer is controversial and varies widely. The terminology is also inconsistent. Based on a survey of gynecologic oncologists, the most common procedure is a superficial (above the cribriform fascia) inguinal lymphadenectomy with (40 percent) or without (34 percent) additional removal of some deeper nodes medial to the femoral vein. Fewer practitioners (22 percent) resect all the deep nodes below the cribriform fascia (Levenback, 1996).

In general, lymphatic drainage from the vulva rarely bypasses the superficial nodes, and a superficial node dissection is adequate for small tumors (see Fig. 31-2). For most others, removal of the deep nodes within the fossa ovalis generally is advisable and may be performed safely with preservation of the cribriform fascia (Bell, 2000). Unroofing the cribriform fascia to remove the deep nodes usually is not recommended because of the unacceptable risks of major morbidity, such as erosion of the skeletonized femoral vessels to the overlying skin flap.

The emergence of sentinel lymph node mapping is a promising modality that has demonstrated vast potential in reducing the radicality of the surgery (see Chap. 31, Sentinel Node Biopsy). (Moore, 2003). However, the clinical implications of this approach and the best technique remain unproven. Groin relapses following a negative sentinel node biopsy emphasize the need for further investigation (Frumovitz, 2004). Implementation of this experimental strategy awaits completion of a prospective Gynecologic Oncology Group study (protocol 173).

Preoperative

PATIENT EVALUATION

Clinical palpation is not an accurate means to evaluate the groin nodes (Homesley, 1993). Magnetic resonance (MR) imaging and positron-emission tomographic (PET) scanning are also relatively insensitive (Bipat, 2006; Cohn, 2002; Gaarenstroom, 2003). Sentinel node identification appears to be the most promising diagnostic test to emerge for excluding the presence of inguinal metastases (Selman, 2005). Fixed, large, clinically obvious groin metastases that appear unresectable should be treated preoperatively with radiation before attempting removal.

CONSENT

Patients should understand the need for unilateral or bilateral groin dissection and its relationship to their cancer treatment. They should be prepared for a potentially several-week recovery in which postoperative complications are common and may include cellulitis, wound breakdown, lymphedema, and lymphocyst formation. These events may develop within a few days, several months, or even years later. In contrast, intraoperative complications are less common, and hemorrhage from the femoral vessels is encountered rarely.

PATIENT PREPARATION

When both groins are dissected, a two-team approach is ideal to reduce operative time. Prophylactic antibiotics may be administered but have not been shown to prevent complications (Gould, 2001).

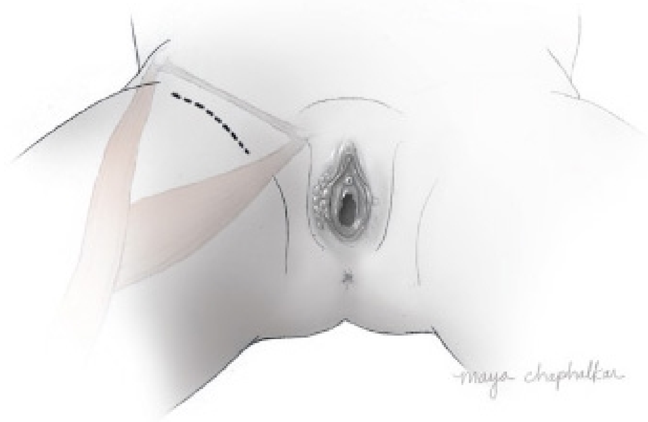
Intraoperative

Surgical Steps

1. **Anesthesia and Patient Positioning.** General or regional anesthesia may be used. Inguinal lymphadenectomy is performed prior to radical partial or radical complete vulvectomy (see Sections 43-22, Radical Partial Vulvectomy and 43-23, Radical Complete Vulvectomy). Legs should be placed in Allen stirrups in low lithotomy position, abducted about 30 degrees, and flexed minimally at the hip to flatten the groin (see Fig. 40-6). Rotation of the thigh a few degrees outward will open the femoral triangle.

2. **Skin Incision.** The groin is incised 2 cm below and parallel to the inguinal ligament starting 3 cm distal and medial to the anterosuperior iliac spineâ€”aiming toward the adductor longus tendon (Fig. 43-24.1). The incision is 8 to 10 cm long and is taken through full skin thickness and 3 to 4 mm into the fat.

FIGURE 43-24.1

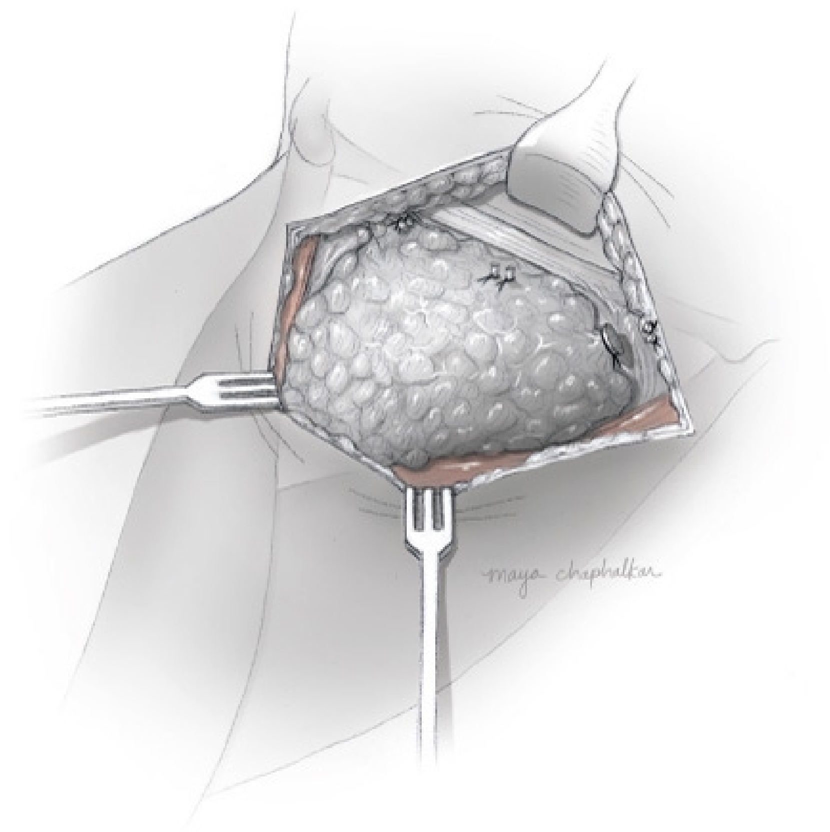


Incisions.

3. **Developing the Upper Flap.** Adson forceps with teeth elevate and provide traction to the dermal surface of the upper skin while a hemostat is opened underneath to begin dissection. Dissection continues down through the subcutaneous fat and Scarpa fasciaâ€”aiming for a position in the midline of the incision 3 cm above the inguinal ligament. Dissection proceeds downward until the glistening white aponeurosis of the external oblique muscle is identified. Adson forceps then are replaced with skin hooks to provide better traction.

   A semicircle of fatty tissue is rolled inferiorly and laterally along the aponeurosis using electrosurgical dissection and intermittent blunt dissection. During dissection, the superficial circumflex iliac vessels are clamped and ligated (Fig. 43-24.2). Additionally, superficial epigastric and superficial external pudendal vessels are clamped and tied as they are encountered (see Fig. 38-3). Dissection proceeds until the lower margin of the inguinal ligament is exposed.

FIGURE 43-24.2



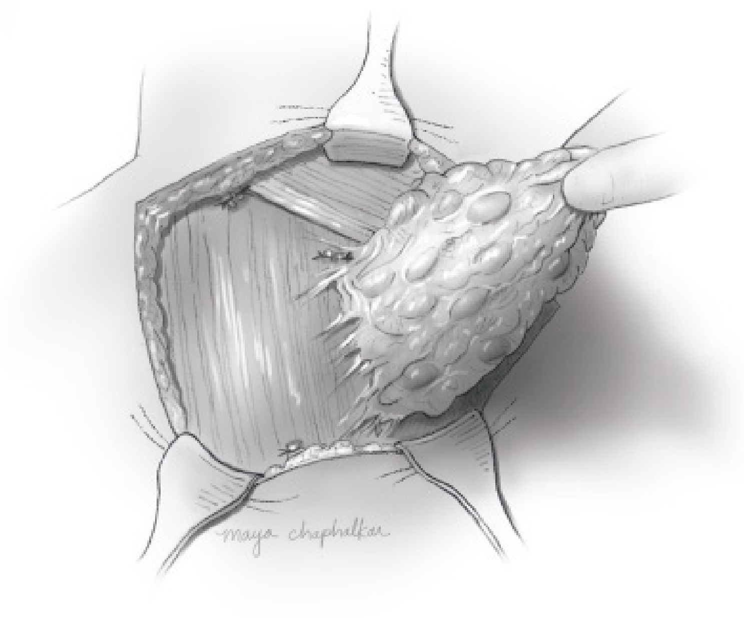
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Dissection of the upper flap.

4. **Developing the Lower Flap.** In a similar manner to the upper flap, the posterior skin flap is raised. Dissection progresses through the subcutaneous fat to the deep fascia of the thighâ€”aiming approximately 6 cm from the inguinal ligament toward the apex of the femoral triangle (see Fig. 38-29). Blunt finger dissection along the inner portion of the sartorius and adductor longus muscles aids development of the lower flap boundaries. The dissection becomes progressively deeper into the subcutaneous tissue of the thigh but remains superficial to the fascia lata. At the apex of the femoral triangle, the converging tissue is divided to completely encircle the fatty-lymphoid specimen. Dissection is continued circumferentially toward the fossa ovalis. Node-bearing tissue is held on traction to aid its dissection. Venous tributaries are ligated as they are encountered.

5. **Removal of the Superficial Nodes.** The superficial lymph nodes lie within the fatty tissue at various locations along the saphenous, superficial external pudendal, superficial circumflex iliac, and superficial inferior epigastric veins (see Fig. 38-29). The saphenous vein is encountered during the dissection of the medial side of the fat pad. The distal end should be individually transected and ligated with permanent suture for identification (Fig. 43-24.3). If desired, it can be salvaged by dissecting it from the fat pad. Circumferential dissection is performed next to isolate and remove the nodal bundle as it exits the fossa ovalis. The proximal end of the saphenous vein should be ligated separately, if sacrificed. Remaining attachments are dissected from the cribriform fascia or clamped and cut to remove the specimen.

FIGURE 43-24.3



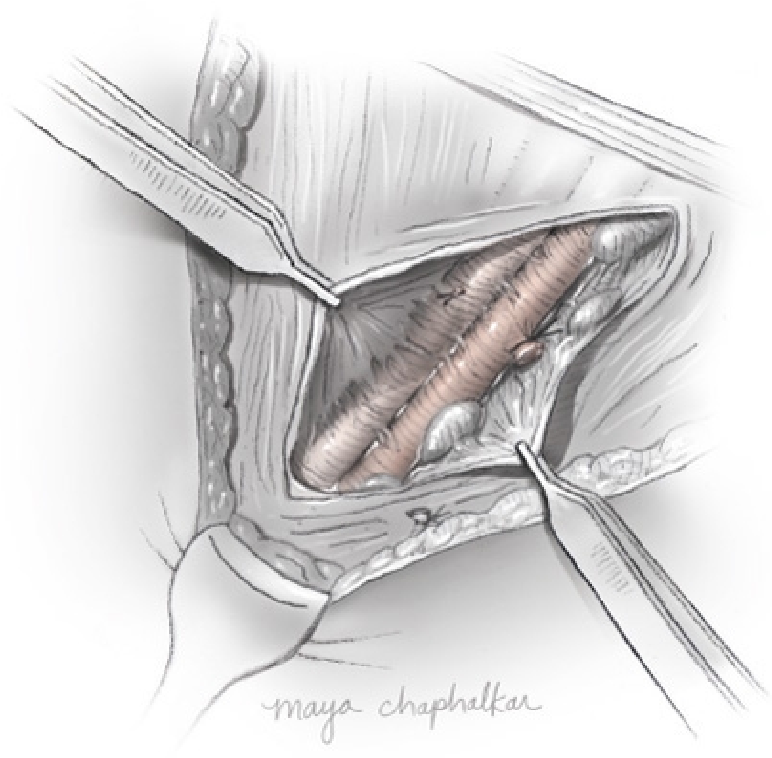
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Dissection of the lower flap and removal of the superficial nodes.

6. **Removal of the Deep Nodes.** The femoral vein should be visible within the fossa ovalis. The deep groin nodes are consistently located just medial and parallel to this vessel. Of these, Cloquet node is the uppermost. The residual deep femoral nodal tissue is excised by removing any fatty tissue along the anterior and medial surfaces of the femoral vein above the lower limit of the fossa ovalis. The femoral sheath and cribriform fascia should remain intact if possible.

   If a clinically positive deep node cannot otherwise be reached, the cribriform fascia may be unroofed by making a longitudinal incision distally along the overlying femoral sheath (Fig. 43-24.4). Seven or eight underlying deep inguinal nodes are revealed, and these deep nodes typically are located in a more orderly fashion than the superficial nodes. Fatty lymphoid tissue then is dissected from the anterior and medial surfaces of the femoral vein. Following node removal, the femoral sheath edges then may be reapproximated using delayed-absorbable suture and/or covered with the sartorius muscle.

FIGURE 43-24.4

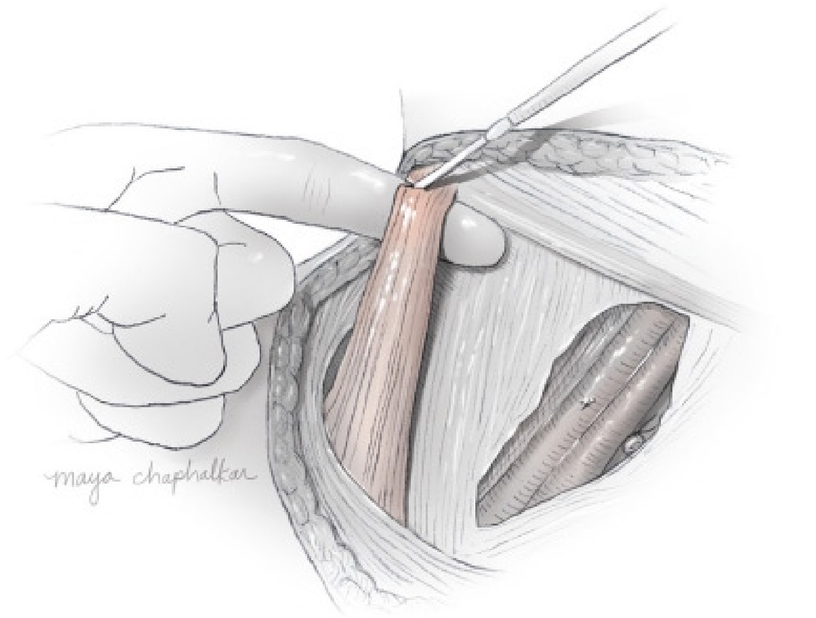


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Unroofing the cribiform fascia to remove the deep nodes.

7. **Sartorius Muscle Transposition (Optional).** The fascia lata is incised to allow blunt dissection of the sartorius muscle (Fig. 43-24.5). The proximal sartorius muscle then is transected at its insertion to the anterosuperior iliac spine. A finger is wrapped around the upper part of the muscle to aid electrosurgical blade transection directly off the spine. Transection should be as high as possible, with care taken to avoid the lateral femoral cutaneous nerve. The muscle then is further mobilized to cover the femoral vessels and sutured to the inguinal ligament with delayed-absorbable suture.

FIGURE 43-24.5

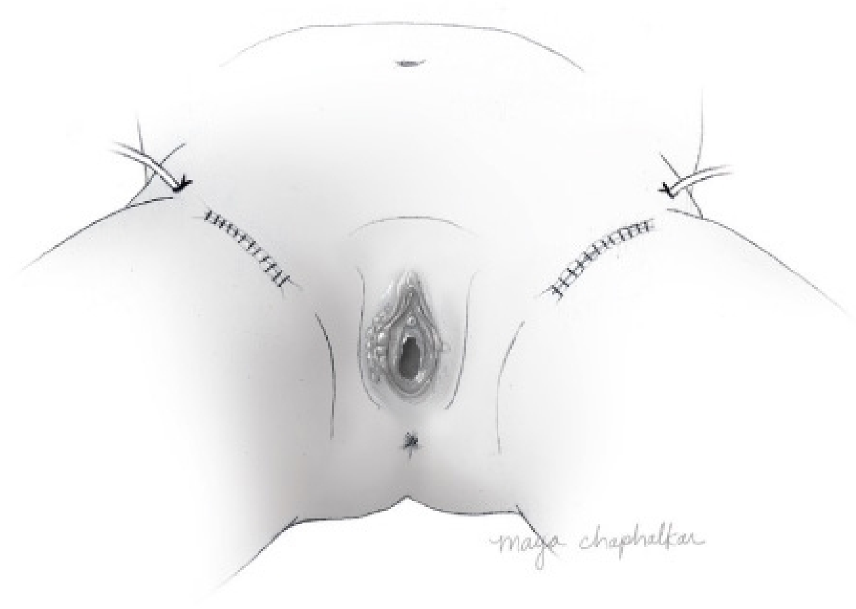


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Sartorius muscle transposition.

8. **Wound Closure.** The surgical defect should be examined carefully, made hemostatic, and irrigated. The groin is closed with layers of delayed-absorbable suture, and a Blake or Jackson-Pratt drain is brought out superolaterally and tied in place with permanent suture (Fig. 43-24.6). Staples are placed to re-approximate skin edges.

FIGURE 43-24.6



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Wound closure.

Postoperative

Suction drainage enables the incision to heal and the underlying space to be obliterated. Drain tubing should be milked manually or stripped regularly with the index finger and thumb toward the suction device to prevent blockage. Drains may be removed when output declines to 20 to 25 mL/day. Typically, this requires approximately 2 weeks (Gould, 2001). Premature removal may result in a symptomatic lymphocyst that requires drain re-insertion or outpatient needle aspiration.

The groin incision should be left uncovered and examined regularly. Postoperative complications are very common, particularly wound cellulitis and breakdown. Preoperative radiation and removal of bulky, fixed nodes increase the risk of these complications. Unroofing the deep fascia also can expose the femoral vessels unnecessarily to erosion or sudden hemorrhage. A protective sartorius muscle transposition may be especially indicated in these selected situations to prevent morbidity (Judson, 2004; Paley, 1997).

Chronic lymphedema is another frequent complication of inguinal lymphadenectomy. In most reports, preservation of the saphenous vein has been shown to reduce the incidence (Dardarian, 2006; Gaarenstroom, 2003). Regardless, this condition typically is much more problematic with the addition of groin radiation. Supportive management is meant to minimize the edema and prevent symptomatic progression. Foot elevation, compression stockings, and on occasion, diuretic therapy may be helpful.

43-25 SKINNING VULVECTOMY

The term *skinning vulvectomy* implies a wide, superficial resection that encompasses both sides of the vulva, that is, a complete simple vulvectomy. A less extensive, unilateral procedure is better referred to as a *wide local excision or partial simple vulvectomy* (see Section 41-15, Wide Local Excision of Vulvar Intraepithelial Neoplasia). The usual indication for skinning vulvectomy is a woman with confluent, bilateral vulvar intraepithelial neoplasia (VIN) type 2 or 3 who is not a candidate for directed ablation with carbon dioxide (CO_2) laser or the Cavitron Ultrasonic Surgical Aspirator (CUSA) (see Chap. 40, Cavitational Ultrasonic Surgical Aspiration). Fortunately, patients with such extensive VIN are encountered infrequently. Paget disease without underlying adenocarcinoma and vulvar dystrophies refractory to standard therapy are other rare indications (Ayhan, 1998; Curtin, 1990; Rettenmaier, 1985).

The surgical procedure is straightforward and removes the entire lesion with negative margins. It is distinguished from a radical complete vulvectomy by removal of only the skin surface with preservation of the subcutaneous fat and deeper tissues (see Section 43-23, Radical Complete Vulvectomy). However, the disfiguring result can be psychologically devastating. In addition, the defect is often large and cannot be closed primarily without a split-thickness skin graft (STSG) or other type of flap (see Section 43-26, Reconstructive Grafts and Flaps).

Preoperative

PATIENT EVALUATION

Prior to surgery, vulvoscopy with directed biopsy is required (see Chap. 31, Lesion Evaluation).These steps exclude an invasive squamous lesion of greater than 1 mm depth, which would warrant a more radical procedure. Familiarity with an array of possible STSGs or flaps is crucial to planning the operation in the event primary closure is not possible.

CONSENT

Patients should be informed that other more limited treatment options either have been exhausted or are inappropriate. The surgery may result in significant sexual changesâ€"which may be permanent. Accordingly, surgeons should emphasize that all efforts will be made to restore a functional, normal-appearing vulva. Fortunately, most physical complications will be minor, such as cellulitis or partial wound dehiscence.

PATIENT PREPARATION

Complete bowel preparation is indicated only if perianal skin is to be excised. Otherwise, enemas are sufficient. Prophylactic antibiotics typically are given. Selection of a donor site for STSG is described in Section 43-26, Reconstructive Grafts and Flaps.

Intraoperative

Surgical Steps

1. **Anesthesia and Patient Positioning.** Regional or general anesthesia generally is required. The patient is placed in dorsal lithotomy position, and adjustments provide access to the entire lesion. Vulvar hair should be shaved. Intraoperative vulvoscopy may be needed to better delineate VIN lesion margins.

2. **Skin Incision.** The inner and outer incision lines are drawn to encompass the disease with margins of at least a few millimeters (Fig. 43-25.1). The clitoris may be spared in many patients by making a horseshoe-shaped incision. If preserving the clitoris, an incision begins at its anterolateral margin and is taken through full-skin thickness at least halfway to the perineal body. Inner and outer skin incision margins are created on both sides of the vulva to completely encompass disease.

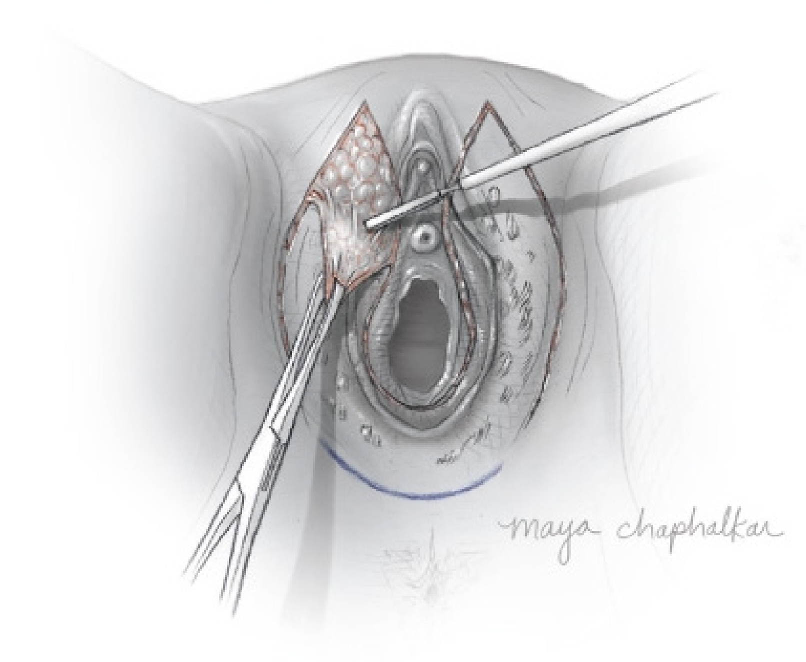
FIGURE 43-25.1

Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Marking the incisions.

3. **Beginning the Dissection.** The specimen edge then may be reflected with an Allis clamp to provide traction as the avascular plane underneath the skin is dissected from the subcutaneous fatty tissue (Fig. 43-25.2). When the anterior skin edge is large enough, a hand is placed underneath to reflect the specimen more firmly and guide dissection inferiorly. The skin incision then is extended downward along the outer and inner incision margins toward the perineal body. Electrosurgical coagulation is used to achieve hemostasis before repeating the process on the contralateral side.

FIGURE 43-25.2



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Performing the dissection.

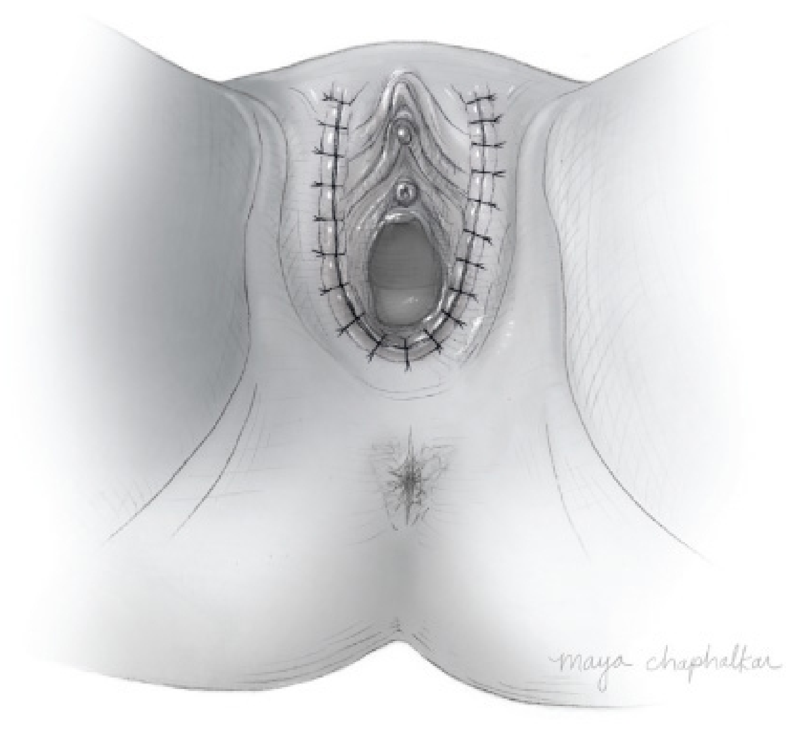
4. **Removal of the Specimen.** The left and right outer skin incisions are joined in the midline superficial to the perineal body. The posterior vulvar tissue is held with an Allis clamp to provide traction for upward dissection toward the inner incision. This portion of the skinning vulvectomy typically is performed last because an avascular tissue plane superficial to the subcutaneous tissue is absent, and bleeding can be brisk. The specimen can be removed following detachment from the inner posterior incision.

   The skinning vulvectomy should be examined carefully to grossly determine the margins. Paget disease or close VIN margins may warrant a frozen section analysis to determine if more tissue requires excision. A stitch should be placed on the specimen to orient the pathologist.

5. **Closure of the Defect.** A dry laparotomy pad is held against the vulvar defect and rolled slowly downward to halt surface bleeding and to aid meticulous electrosurgical coagulation of vessels. The operative site is irrigated and assessed.

   If the width of the defect is sufficiently narrow to permit primary closure, the surrounding tissue is mobilized. Lateral undermining may be particularly useful for a tension-free closure. Vertical mattress delayed-absorbable sutures then are placed circumferentially with the knots positioned laterally (Fig. 43-25.3).

FIGURE 43-25.3



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Primary closure.

6. **Final Steps.** A CO_2 laser may be used to vaporize multifocal lesions outside the operative field.

Postoperative

If a primary closure is performed, postoperative care is essentially the same as described for patients undergoing radical partial vulvectomy (see Section 43-22, Radical Partial Vulvectomy). Long-term surveillance is mandatory regardless of margin status to identify recurrent or de novo sites of preinvasive disease (Rettenmaier, 1987).

43-26 RECONSTRUCTIVE GRAFTS AND FLAPS

Primary closure of a vulvar wound typically is not advised if closure of a large defect would create excessive incision tension or if other wound factors are present. In these cases, placing a reconstructive skin graft or flap is preferred to allowing a defect to heal by secondary intention. In general, the simplest procedure that will achieve the best functional result should be selected.

The decision to perform a split-thickness skin graft (STSG), lateral skin transposition, or rhomboid skin flap depends on clinical circumstances and surgeon experience. Variations of these techniques are used commonly in gynecologic oncology (Burke, 1994; Rettenmaier, 1987).

Typical candidates for a skin graft or flap have undergone a large wide local excision, skinning vulvectomy, or partial or complete radical vulvectomy. Myocutaneous flaps, most commonly using the rectus abdominis and gracilis muscles, are used primarily in patients with prior radiation, very large defects, or a need for vaginal reconstruction. However, a full description of the innumerable

types of local flaps is beyond the scope of this section.

Preoperative

PATIENT EVALUATION

Fortunately, a broad range of operative procedures is availableâ€”each with its advantages and disadvantages (Weikel, 2005). The size of the lesion and the anticipated postoperative defect largely will dictate reconstructive options. In some complicated cases, plastic surgical consultation may be indicated.

CONSENT

Many women's body image will be altered significantly following extensive vulvar surgery, and sexual dysfunction may be problematic (Green, 2000). When discussing these effects, patient responses vary widely. Some express minimal concern, whereas others are devastated by the thought of a disfiguring result. Accordingly, counseling is individualized, specifically addressing patient concerns.

In addition, wound separation, infection, and wound healing by secondary intention are common complications. Moreover, patients also should be advised that their disease may recur within a graft or flap (DiSaia, 1995).

PATIENT PREPARATION

Complete bowel preparation generally is indicated for most reconstructions. Because a patient may be relatively immobile postoperatively and the need to prevent wound contamination is absolute, enemas usually are insufficient. In addition, prophylactic antibiotics typically are given. Early ambulation may be detrimental to graft or flap healing. Therefore, to prevent venous thrombosis, use of pneumatic compression devices or subcutaneous heparin is warranted.

For patients undergoing STSG, the hip, buttock, and inner thigh should be examined carefully. The selected donor sites should contain healthy skin, be hidden by the patient's clothing postoperatively, and be accessible in the operating room. Typically, a graft is taken from the upper thigh.

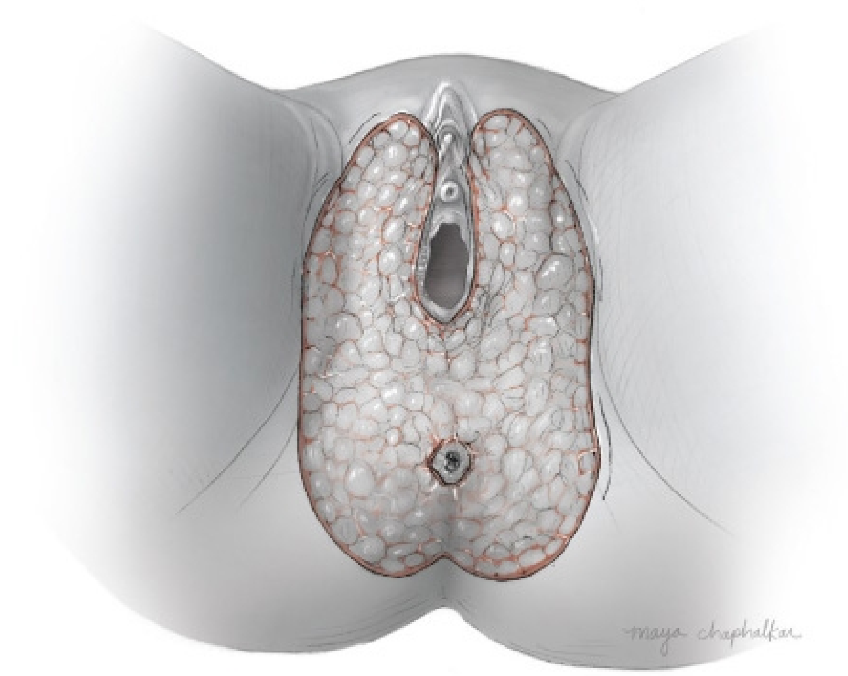
Intraoperative

Surgical Steps

1. **Anesthesia and Patient Positioning.** General or regional anesthesia is required. The patient will need to be positioned in dorsal lithotomy position with complete access to the vulva, upper thighs, and mons pubis. Sterile preparation of the lower abdomen, perineum, thighs, and vagina is performed, and a Foley catheter is placed. Infrequently, the buttock or hip will be selected as the STSG donor siteâ€”this will require additional repositioning.

2. **Evaluating the Surgical Defect.** After the vulvar resection has been completed and hemostasis is achieved, the wound is examined to confirm that primary closure is impossible (Fig. 43-26.1). The best graft or flap that will cover the defect adequately is determined.

FIGURE 43-26.1

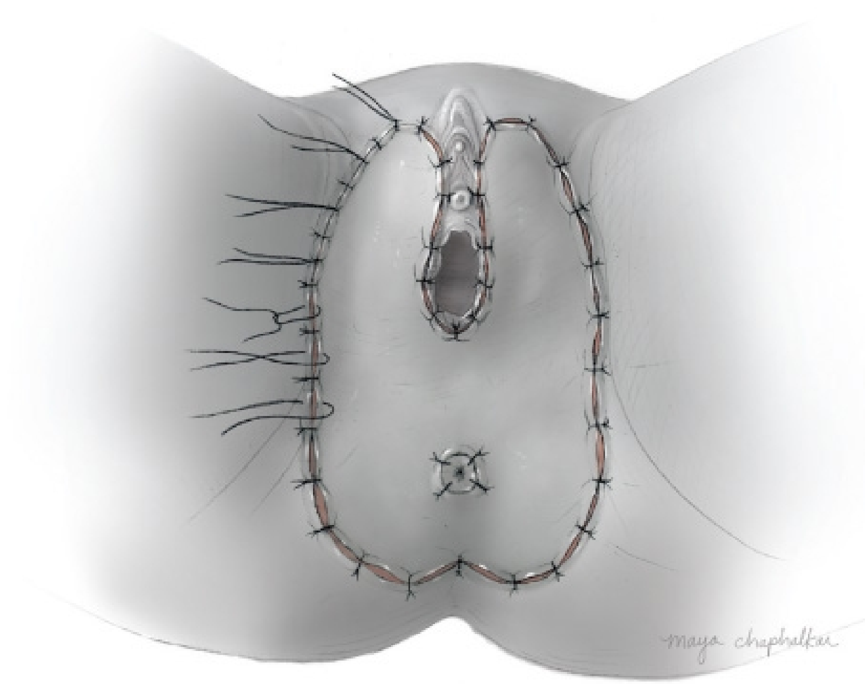


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Large vulvar surgical defect.

4. **Split-Thickness Skin Graft (STSG).** An electrodermatome is required to harvest the graft from the donor site when performing a STSG (see Fig. 41-12.1). At a setting of 0.018 to 0.022 inches thick, normal epithelium is harvested from the donor site. The STSG is placed in a basin and moistened with saline. The donor site then is sprayed with thrombin, covered with a transparent film dressing (Tegaderm, 3M, St. Paul, MN), and wrapped firmly with gauze. The recipient site is irrigated with antibiotic solution, and hemostasis must be absolute. The graft then is held over the defect and cut to fit so that there is some overlap. Meticulous care is required to smooth graft wrinkles and avoid graft tension. Edges then are sutured to the skin with interrupted 3-0 nylon suture (Fig. 43-26.2). Moistened gauze or cotton balls are placed over the graft and covered with opened and fluffed gauze squares to provide light pressure. To create a stable dressing, a few ties usually are placed through the covering dressing and lateral to the graft site.

FIGURE 43-26.2

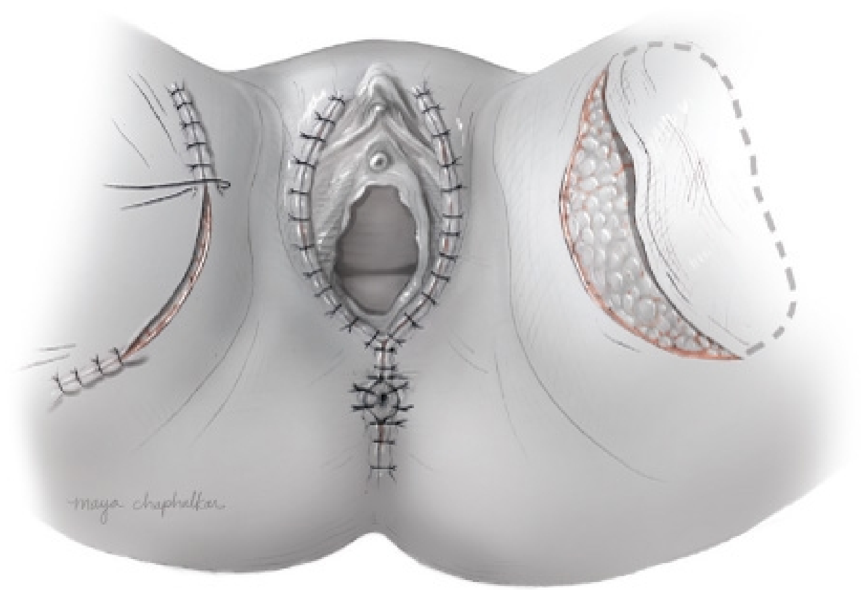


Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Split-thickness skin graft.

5. **Lateral Skin Transposition.** The skin lateral to the surgical defect is undermined extensively, and separate relaxing upper thigh skin incisions are made bilaterally. The resulting mobility of the vulvar skin should allow for a tension-free closure using interrupted vertical mattress sutures (Fig. 43-26.3). The relaxing incisions are separately undermined laterally and closed in similar fashion.

FIGURE 43-26.3



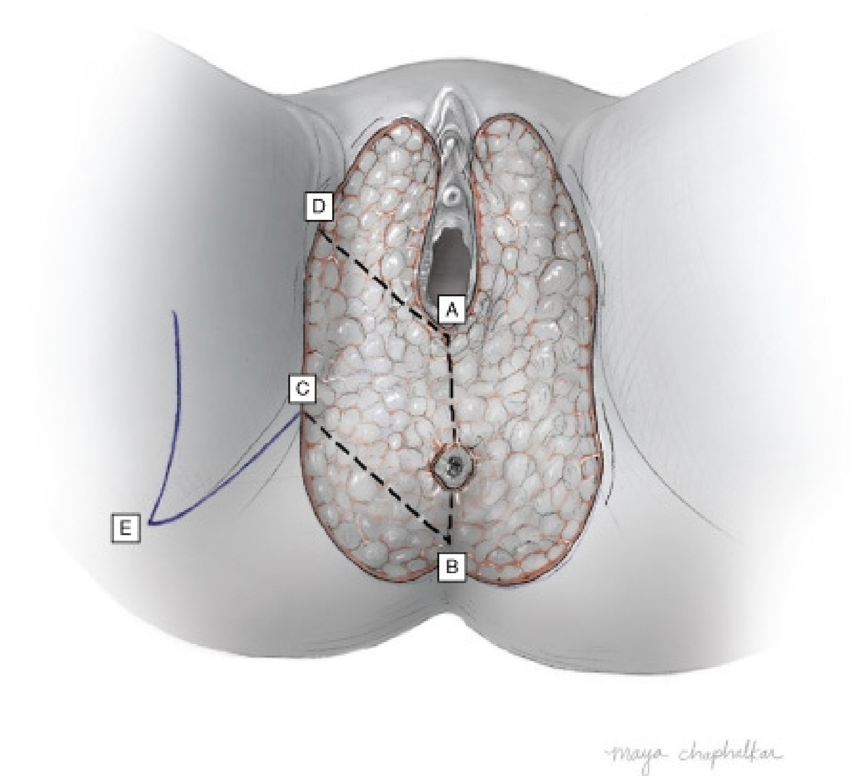
Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Lateral skin transposition.

6. **Rhomboid Flaps.** A rhomboid is a four-sided parallelogram with unequal angles at its corners. When creating a rhomboid flap from adjacent tissue, a marking pen is used to draw all sides the same length as the short axis of the defect (*A-C* in Fig. 43-26.4). This minimizes wound tension and prevents necrosis. The diagonal *A-C* is continued in a straight line onto the adjacent vulvar skin lateral to the defect and marked so that the length of *AC = CE.* The remaining rhomboid sides are drawn in parallel.

   Incisions are made through the skin and into the subcutaneous fat. A flap is developed to include underlying fatty tissue and is mobilized medially to cover the surgical defect. Skin edges then are re-approximated with vertical mattress stitches using delayed-absorbable suture (Fig. 43-26.5). Typically, excess tissue at the corners requires trimming to provide a smooth contour. A suction drain is placed at the donor siteâ€"this area usually can be closed primarily without tension.

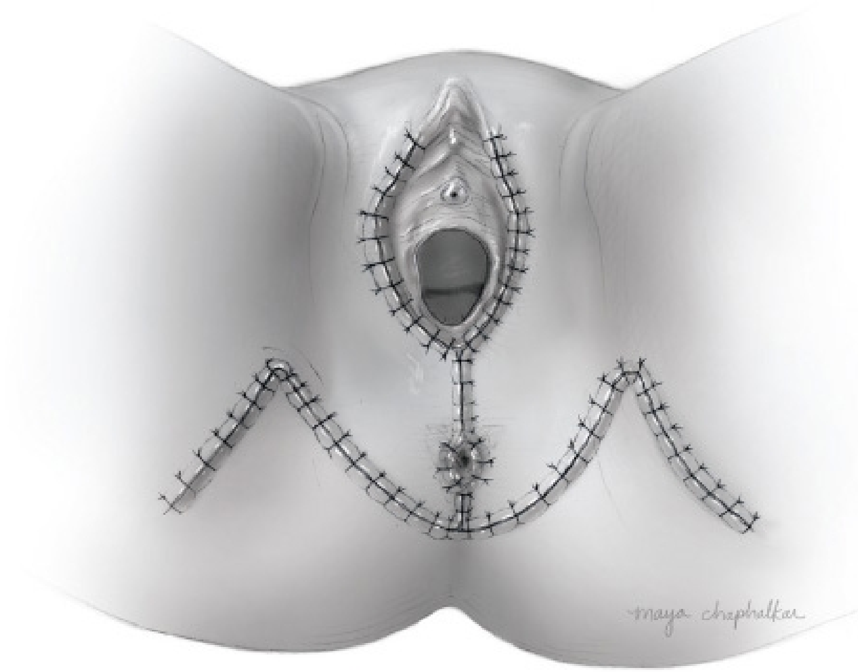
FIGURE 43-26.4



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Rhomboid flap: incisions.

FIGURE 43-26.5



Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: *Williams Gynecology*: http://www.accessmedicine.com

Rhomboid flap: closure.

Postoperative

Patients should be kept relatively immobile for the first 5 to 7 postoperative days to prevent tension on the reconstruction. A low-residue diet, diphenoxylate hydrochloride (Lomotil, Pfizer, New York, NY), or loperamide hydrochloride (Immodium, McNeil PPC, Fort Washington, PA) tablets will aid healing by delaying defecation and prevent straining (see Table 25-5). Thromboembolic prophylaxis should be continued until the patient is ambulatory (see Chap. 39, Prophylaxis Options).

During the first few days postoperatively, the wound should be examined frequently to identify signs of hematoma or infection. For STSGs, the transparent dressing may be removed from the donor site after about 7 days and an antibiotic ointment applied. For skin flaps, positioning changes or release of some sutures may be helpful if ischemia is noted at the margins. Suction drains are discontinued when output is less than 30 mL per 24 hours.

Women experience significant sexual dysfunction after vulvectomy. However, the extent of the surgery and need for reconstruction are less important than pre-existing depression and hypoactive sexual dysfunction. Accordingly, postoperative psychological counseling and treatment of depression may be particularly helpful (Green, 2000; Weijmar Schultz, 1990).

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